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Section of Surgery

President—JOHN BRUCE, C.B.E., T.D., F.R.C.S.Ed.

[*October* 12, 1955]

Changing Concepts in Contemporary Surgery

PRESIDENT'S ADDRESS

By JOHN BRUCE, C.B.E., T.D., F.R.C.S.Ed.

FOR my subject I have chosen to glance at some features of the contemporary surgical scene and have found the exercise instructive, for there is no doubt that we who follow the craft of surgery are living in exciting and interesting times. Indeed, in the last two decades there has been a revolution in surgical practice and surgical thought; and while we can all of us appreciate the influences at work, we cannot all assess fully their impact on surgical organization and teaching. In any event, a glimpse at the horizon is seldom without reward; and I pretend to no more than that this is a personal reconnaissance.

The golden age of surgery was born with the twin discoveries of anæsthesia and antisepsis. Then it was that surgery was raised from a lowly—and sometimes not quite respectable—craft, to the dignity of an art and a science. Before, the surgeon's concern was with injuries, amputations and superficial growths; after, most of the anatomical barriers were crashed, and most of the pathological frontiers assaulted, until in 1935 no less a master than Lord Moynihan could claim that surgery had reached its zenith; there were no other worlds to conquer. Paré had said much the same thing in 1575; "Posterity", he wrote, "will not be able to surpass us (be it said without malice or offence) save by some additions, such as are easily made to things already discovered." Others, following on, had also succumbed to the temptation of gloomy prophecy.

There was perhaps some excuse for Moynihan. With the new weapons at hand, only the most vital structures had escaped the assault of surgical craftsmen who will never be surpassed in courage or in brilliance; and in the process, a tremendous stimulus had been given to the whole of medicine in general, and in particular to the twin sciences of anatomy and pathology which were then the very foundations of surgery. There was a demand for a precision in anatomical study which had not existed hitherto; the localization of cerebral and spinal function, the intimate arrangement of the bile ducts, the functional anatomy of blood vessels and lymphatics, and much else stems from this. The extension of operative surgery, to the abdomen in particular, permitted and encouraged the observation of disease under novel conditions, and at formerly unsuspected stages. It was no longer necessary to interpret clinical states against the background of the terminal pathology of the post-mortem room. Now was born the "pathology of the living", and early clinical manifestations of disease began to be correlated with early anatomical changes.

It was amongst surgeons themselves that the need for re-orientation of effort was recognized. Superlative techniques and superb courage had advanced the art and craft of surgery a long way on the road to perfection; but not to the zenith, as Moynihan had supposed. The challenge of the "forbidden territories", the failures of immaculate surgery, the mortality and morbidity of operation were the spurs to further progress. There was a shift in emphasis from technique to patient, from the mechanical to the biological, from the art to the science. The death knell of surgical empiricism had begun to sound. To-day we are the nearest heirs of a great tradition; and not the least part of our inheritance is the knowledge that in these days of high surgical adventure, surgery quickened the tempo of discovery and advance in medicine, and in all the sciences ancillary to it.

The direct consequence is that surgery has now acquired an additional prop. Just how precarious was the earlier two-pillared foundation of anatomy and pathology is only apparent now that physiology—in its broad sense—has been brought in as third leg of a tripod; for without detracting in any way from the essential and permanent importance of the older disciplines, the "new look" of contemporary surgery is physiological. The roots of the new knowledge are deep, though the flowering has taken an unconscionable time. The ability of man to survive injury, surely the foundation of the practice of surgery, must have excited wonder and speculation since the dawn of time, but it was not until long after Claude Bernard had defined the "milieu intérieur", and long enough after sepsis and hæmorrhage—the most obvious of the "injuries" to which operation exposed the patient—had largely been conquered, that Leriche propounded his concept of a "maladie post-opératoire", a train of effects inseparable in some degree from every act of surgery, and for whatever cause. The quality of these achievements is remarkable. The last of the great

anatomical barriers—the heart, the chest, the liver and the pancreas—have yielded; some of the remaining pathological frontiers have been breached—e.g. malignant disease of the gullet and the lung, the congenital and deforming lesions of the heart and vessels. Surgical adjustment of disordered function and of endocrine status—though relatively in its infancy—is already a commonplace and accepted concept. But most important of all—the general practice of surgery has found a new safety, and in consequence a greater range of usefulness and application.

Many hands have shared in refashioning the face of surgery; for as of right we surgeons have levied a tribute—of idea, of technique, of material—from any source with which we have been in contact. But I believe that in the final synthesis, the contribution of our own craft has been outstanding. Indeed the basic skeleton of the new surgery was perceived and defined by surgeons; some—and not the least important—parts of the flesh have been modelled by the labours of the surgeon-physiologist both in hospital and in laboratory; and in the ultimate embellishment, ours has been the obligation of translating to practical use the discoveries of the physiologist, physicist, chemist and bacteriologist. Our debt to the basic sciences is real and heavy; but true to our great tradition, we have repaid it by giving a tremendous fillip to the whole science of medicine, so that there is scarcely an activity that has not been enriched and expanded by contact with the surgeon.

At the moment it is probably true to say that the gross physiological and metabolic derangements that beset surgery are understood and appreciated. The steady fall in the number of deaths following operation is an index of this; that so many of our activities are accomplished without anxiety and without complication is one of the inspiring features of the surgery of to-day. Indeed it is the progress of the disease, or the vagaries of the pathology that now determines the outcome of surgery more often than the hazards of the operation itself. There are still worlds to conquer in some of the special fields—the surgery of the heart, the great vessels, the brain; but signs are not wanting that success is only round the corner.

But if in broad outline the physiological and biochemical effects of surgery are reasonably clear, there is still much to be learnt of the intimate detail; and much to be elucidated when the responses are morbid as a result of disease. These further quests are likely to lead us into deep waters—to the complexities of cell structure and behaviour, to the realms of enzyme chemistry, to the influence of the endocrine system on body function in disease and after operation. That these researches will have far-reaching effects on surgical technique—at least on "general surgical" technique—is hardly likely. That they will have an important influence on surgical thought and surgical results is certain, for there should emerge from them new concepts, not of disease, but of the vital mechanisms through which disease in general operates, of the cellular derangements that constitute disease.

I believe that we may even now be at the beginning of a new era in surgery—a pathological era, pathological in a new sense, a new pathology based not on the relatively crude observations that have served to date, but on the studies of cellular derangements that the new weapons of science—histo-chemistry, the electron microscope, the ultra centrifuge, and tissue culture—have placed in the hands of research workers.

But concepts and ideas are changing, not only in the clinical practice of surgery, but in respect of surgical organization, research and teaching. This is the era of the specialist, and specialization has been an inevitable development. The growth of knowledge and the evolution of diagnostic and therapeutic techniques have made the mastery of all surgery by a single individual impossible, and division of interests and responsibilities is the logical outcome. Already the rewards are substantial, not only in the advancement of knowledge, but in the better clinical care of the patient and the increased safety of operation.

But have we considered all the possible—perhaps the probable—implications? In particular, where does general surgery stand in the scheme of things to-day? Is it not an outmoded concept, a subjective concept, a tag that many of us only continue to apply to ourselves because we happen to treat diseases of more than one of those systems not yet recognized as specialties? In this sense it seems to me quite illogical. "General" surgery ought to be the body of knowledge that is common to all the branches of surgery, that is, indeed, the basis of all surgery—the healing of wounds, the infections, anæsthesia, the metabolic and systemic effects of surgery, and the like. It should therefore be equally the concern of all the subdivisions of surgical practice. In truth the so-called "general surgeon" of to-day is largely an abdominal surgeon, at least in the teaching hospitals and in the large centres. It follows that, provided he is well founded in the real content of general surgery, i.e. in the scientific basis of all surgery, it is illogical to insist that aspirants to the specialties must serve an apprenticeship in the wards of the general surgeon. He could stick to his own last, without detriment either to his prowess or his value. It would be necessary radically to alter the scope and arrangement of our qualifying examinations, and to review our methods of training if this were accepted. But the trend is even now apparent.

Fifty years ago when this Society was born, the programme of the Surgical Section included everything that could be regarded as surgery save gynæcology. To-day it is unusual to see a urologist, an orthopædic surgeon, or a neurosurgeon in our midst except by special invitation; and even the proctologist, the thoracic surgeon and the plastic surgeon have left their parents' house. In turn, few of us foregather at the conclaves of the specialists; and fewer and fewer of us are familiar with their problems and their points of view. It follows that we can offer little of intellectual or practical value to the embryo specialist that he should not be able to acquire within the ambit of his chosen discipline.

Specialism has other problems. Restriction of activity to one area or system is no longer dictated only by the intellectual content or the research needs of the specialty, but by therapeutic demand. The effect of this is to overwhelm the specialist with repetitive work, and to leave him little time, or leisure, for exploring and exploiting the frontiers of his subject. It has been suggested that, having defined the problems, and having found the solutions, the specialist should return much of the content of his specialty to the "general" surgeon. I cannot see this happening; and if we subscribe to the new interpretation of "general surgery", there is no reason why it should. But just as specialism grew from a desire to explore some selected problem of surgery in general, so we may yet see arise within the specialties of to-day subspecialties where pioneers are mainly concerned with the further advancement of knowledge.

It seems likely that in time the growth of specialism will lead to a critical scrutiny of the geographical segregation within our hospitals of the surgeon and the physician. The reasons for this separation are obvious, and no doubt were once cogent, for medicine and surgery were separated by more than tradition. Each discipline dealt with its special and differing problems. There was a time when intrusion by surgeon or physician into the other's supposed territory was fraught with danger—as was the case in gastro-intestinal bleeding, in jaundice, in ulcerative colitis, and so on. But the surgeon and the physician are now more and more concerned with the same clinical problems, and each brings to them his own particular approach, diagnostic or therapeutic. But in many cases, neither sets himself up as an ultimate judge; and increasing and intimate clinical co-operation is one of the happiest features of the modern scene. It seems a logical extension of this to revise the concept of medical and surgical divisions at the opposite ends of the hospital. Are not units under the joint direction of physician and surgeon more promising under modern conditions? Such a unit may well have surgical and medical departments, geographically proximate; but the patient would have the inestimable benefit of a "team" approach at every stage of his hospital stay.

For long the palpable untruth has been proclaimed—mainly by surgeons—that the surgeon is a physician who operates. If this were ever true, it is certainly not so now, when the techniques and the apparatus of investigation available to the physician have advanced as much as the techniques and the apparatus of surgery. The obligations of both physician and surgeon have become increasingly exacting, and certainly the busy surgeon has little time to undertake the burden of physiological study that must go to the pre-operative investigation, and the post-operative care of his most interesting and most difficult cases. Those who affect to despise the concept of the clinical "team" in the event have usually to delegate important investigations to house officers or laboratory technicians. In my experience, the intimate association in our work of medical colleagues of equal standing pays a richer dividend; and it has been interesting to find the physician, brought into closer contact with surgery, becoming more aggressive as the surgeons grow more conservative.

A "unit" system of bed allocation in our teaching hospitals would naturally have important repercussions on the instruction of medical students. The student now acquires his knowledge in a series of layers—here a slab of surgery, there of medicine; and though the composition of the slabs is comparable—for gall-stones, duodenal ulcers, thyrotoxicosis, hypertension, bronchial carcinoma are precisely the same diseases in the medical as in the surgical wards—the different bias with which each slab is laid serves to create in the student's mind a conviction that treatment may be a matter either for the physician or for the surgeon. Instruction in units where cases are treated, some by medical methods only, some by surgery as well, but in both cases after joint appraisal, and where the surgeon and physician share the teaching, seems to offer something more logical than we have at present.

It is possible to discern a new attitude to surgical teaching, even in the great strongholds of undergraduate medical education. The obligation of the undergraduate instructor in surgery is mainly to teach the elements of surgical diagnosis, and the scope and the possibilities of surgical therapy. The technical aspects of surgery have become entirely a post-graduate study; and a view is gaining currency that some re-orientation of the functions and organization of our great teaching hospitals is perhaps necessary to give effect to this. At least in the provinces, there has been a tendency since the war to preserve the teaching hospitals for undergraduates, and to restrict their clinical activities mainly to "general

surgery". In consequence, the specialist units have been dispersed and displaced to the geographical periphery, partly from a reluctance to disturb the established order, partly from an unwillingness to offend vested interests, and partly because beds for special purposes were easier to come by away from the main centre.

The effects of continuing such a policy may well be disastrous. For the most part it is in the specialized units that the frontiers of surgery are being advanced, that the tempo of investigation and discovery is quickest. Such units must be an integral part of the main teaching hospital; it is difficult to preserve its prestige and its status if it degenerates into a sorting house for the onward transmission of the most interesting and most fruitful kinds of surgical work.

I believe this danger threatens particularly the great University Hospitals of the provinces, where the immediate post-war concept of the undergraduate University Hospital appears to have taken firm root. It would be a good thing—and it may not be too late—to think again. For not only does dispersion of the special units impoverish the teaching hospital, it reflects on the attitude and the opportunities of the specialists themselves. The corollary, of course, is plain in respect of surgery; the University Hospital should have as great an obligation to teach postgraduates as undergraduates, if indeed its post-graduate function should not be regarded as its supreme purpose.

Finally, what of the training of the surgeon-to-be? This is a matter, not for a mere comment but for an essay. Surgical education by apprenticeship, by precept and by example, has served us well in the past, and is likely to remain the pivot on which our educational policy revolves. Apart from that, we should be careful not to lay down any hard and fast rules. Already the orderly and automatic progression implicit in the Health Service "ladder" is tending to stifle enterprise; and it is time to return to a system in which those with the ambition and the capacity for surgery are encouraged to make their own plans for the acquisition of knowledge and experience. Economic difficulties, and the fear of losing ground in the local race, are reducing the movement of our young people between countries, and cities and even units. We are in fair danger of turning our pupils out from a common mould, in a common shape, and with a common background. The young surgeon of to-day must be better grounded than ever before in the basic sciences, if he is to bring to the practice of surgery the biological attitude it demands. He must acquire an eager curiosity, and a divine discontent, so that he can recognize the unsuspected problems, and define the chinks in the armour of surgery. He must possess the "experimental" outlook; but this does not mean that he need spend years at the laboratory bench. The clinical science of the ward and hospital afford plenty of opportunity for indulging what is, after all, no more than an attitude of mind; the ability to state a problem, to evolve a hypothesis, to submit it to controlled investigation, and to draw the appropriate conclusions. No greater emphasis should be placed on service in the experimental laboratory than on training in clinical investigation, or service in the anatomy rooms or the pathological department.

In this country, in the past years, there have been three portals through which the young man could attain to a surgical career—the anatomical, the pathological and the physiological. There is every reason to keep all these doors wide open, for surgery needs all its props, and there is still much to be garnered from the older fields. The revelation of the segmental structure of lung, of liver and of kidney with its profound practical implications is an example of this, and there are many others.

To the enquiring and intelligent surgical trainee research—the constant quest for knowledge, for the elucidation of problems—should be a continuous and unremitting part of the daily round; the questioning attitude should be part of his stock-in-trade. The place of Research, with the capital initial, and of Research Years, is more difficult to define. Not all surgical aspirants are intellectually or emotionally suited to the laboratory bench or the physiological or biochemical laboratory; and research under compulsion, or for the material reward it may bring, is generally without virtue. Nevertheless it is our obligation to watch for, and encourage, any special aptitude for it in those whose surgical footsteps it is our privilege to guide. But we should be clear about its scope and object.

The activities of the so-called experimental surgical laboratory are often largely physiological, with a doubtful relationship to surgery. For the surgeon in training, however, it is one method of acquiring a scientific outlook, and provided he has sufficient time also to learn well the practical side of his craft, it is valuable.

But the large problems of surgery yet unresolved are complex and fundamental. They demand—and deserve—the active participation of sciences that have themselves made enormous strides in the post-war years. The young surgeon at best can only acquire a superficial acquaintance with these sciences; and though he may sometimes convince himself—and others—that his researches in foreign fields are important, they seldom withstand the critical scrutiny of the trained scientist.

There are two ways in which the fundamental research of surgery may be conducted,

apart from the unpredictable appearance of another genius such as Lister. We can import into our surgical laboratories the appropriate scientist. If he is simply seconded from his own stamping-ground for a specific reason and a specific period, this works well. If not, he is generally not in the first flight; and segregation from his own kind, who speak his own language, ensures that he never gains the first flight. The research in consequence is often second rate, and "suspect". In the great teaching places, the proximity of great scientific departments and distinguished scientists makes isolation not only unnecessary but wrong. The young surgeon with an impulse for scientific investigation can learn much from attachment to such departments; and it is necessary for the progress of surgery that some of our surgeons should be so trained. It is unlikely that these will acquire the clinical experience or the operative facility of their contemporaries; but to them will fall the privilege of interpreting the discoveries of the basic sciences in a clinical context, and of translating them into clinical practice.

To a few may come the opportunity of high personal contribution, with all the intellectual satisfaction that derives from it. The value of these surgical scientists is no less than that of the distinguished clinician or the most accomplished surgical craftsman, and, in the surgical scheme of things, no more. In the past we have generally left them to find their recompense in the interest and the value of their research; in a more enlightened day their reward should be no less material and no less substantial than that of their colleagues who derive equal satisfaction from the ward and the theatre.

And so I come to the end of this rapid glance at some of the problems of contemporary surgical practice and thought. What meets the eye is heartening. We live in a great age—perhaps the most momentous so far in the long story of mankind—a great age in which nothing is static for long. But both as an art and a science, surgery is more than holding its own, while yet remaining constant to its chief privilege and its principal charge—the loyal service of mankind in affliction.

[*March* 7, 1956]

DISCUSSION ON SURGICAL ASPECTS OF DISORDERED CALCIUM METABOLISM

Dr. C. E. Dent:

General Aspects of Calcium and Phosphorus Metabolism with Especial Reference to Surgical Problems

Before dealing with a few of the more surgical aspects it is necessary to describe very briefly some general considerations of calcium and phosphorus metabolism. I propose to try to work out the possible reasons whereby there may be changes in plasma calcium and phosphorus levels, these being the only measurements that it is possible to do frequently.

In the case of the plasma (or serum) calcium level, it is helpful to appreciate that this is maintained in normal circumstances at between 9–11 mg./100 ml. Only slight deviations from the normal range are tolerated and if they occur they may produce severe symptoms and disease. This accurate maintenance occurs in spite of a very rapid dynamic equilibrium between the relatively small amounts of calcium in extracellular fluids and the very much larger quantities in bone. I have tried to summarize the situation in Fig. 1, where arrows indicate the factors simultaneously operating which tend to raise or lower the plasma calcium level and which are normally very cleverly balanced. Note that the daily net absorption of calcium from the food is only comparatively small—about 150 mg. in adults—and that if no bone growth is taking place while plasma levels are maintained this same quantity must be lost in the urine. Because these quantities are small compared with the quantities of calcium in extracellular fluid and even more in bone, it is obvious that very acute changes in plasma calcium level cannot be brought about by acute changes in either of these factors but must indicate a disturbance of the equilibrium between the plasma level and bone. This is the first basic fact to appreciate. There is an exception to this rule which is of limited importance, so it is shown as a dotted arrow in Fig. 1. This relates to the rapid onset of marked uncompensated calcium loss in the milk at the beginning of lactation. In domestic animals, such as cows, this may be severe enough to produce tetany—the so-called "milk fever". A further fairly acute drain on the calcium reserves in bone occurs in the rapid phase of antler growth of stags. On the other hand, however, more chronic changes of calcium level can indeed be induced by long-term changes in any or all of these factors.

The next point is that any such chronic disturbance of plasma calcium level needs to be further studied with the view to determining where the disorder of equilibrium has occurred. The urinary output is readily determined and should be measured more often than usual.

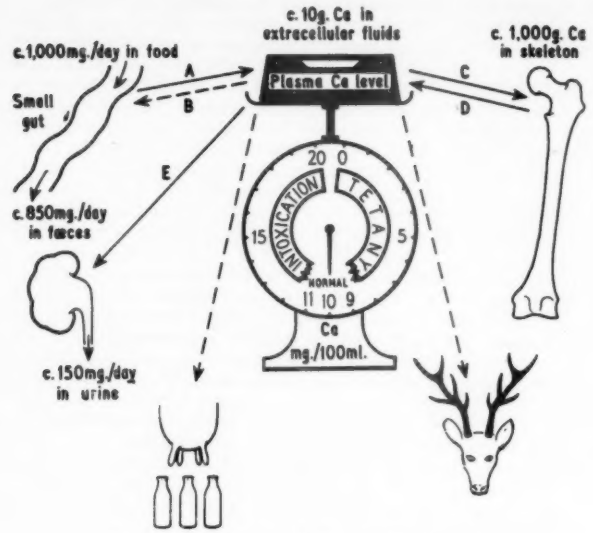

FIG. 1.—Calcium metabolism and transport.

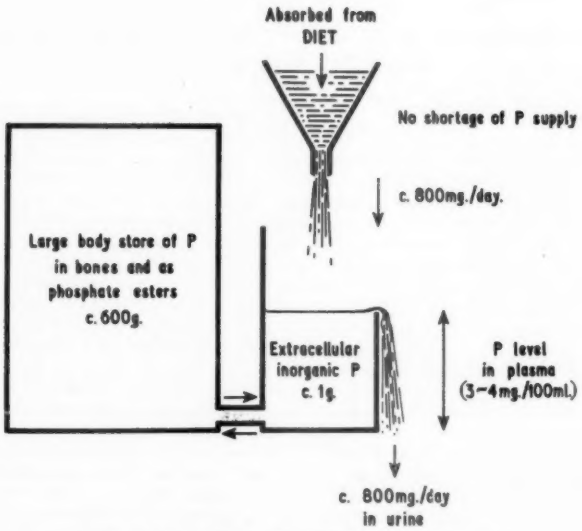

FIG. 2.—Phosphorus metabolism and transport.

On the other hand, absorption of calcium from the food is difficult to measure since it requires analyses of diet, as well as of stools, which need to be carried out for about two weeks or so if they are to have any meaning. However, if this is also done then we can determine indirectly the very important equilibrium between plasma calcium and bone calcium since a gross change of this in either direction is the calcium balance—namely the difference between total dietary intake and total excretion in urine and stools. Our rule here is a very simple one—"What goes in must stay in or come out". This balance measurement can be made very accurate, and it tells us just what is happening to the patient's bones at

that time. This is because of the fortunate fact that nearly all the body calcium is present in the bones, only negligible quantities being in the soft tissues or extracellular fluids.

There is no time to deal in detail with the various factors which can and do exert a continuous influence on calcium metabolism and transport. In Table I, however, many of these are summarized.

TABLE I.—FACTORS WHICH INFLUENCE THE DYNAMIC EQUILIBRIUM OF CALCIUM IN THE BODY
(Capital letters refer to arrows shown in Fig. 1)

(1) Equilibrium A+B is moved over to the right, i.e. more calcium moves grossly from the gut to raise the plasma calcium level, by—
- a. high calcium intake.
- b. acidity of gut contents.
- c. large doses of vitamin D (this action is antagonized by cortisone).
- d. small doses of vitamin D in certain individuals who are over-sensitive to it (this action is antagonized by cortisone).
- e. the presence of peptides in the gut (from dietary protein).
- f. youth.

(2) Equilibrium A+B is moved in the direction of less supply of calcium from the gut to the blood stream by—
- a. low calcium intake.
- b. deficiency of vitamin D.
- c. hereditary conditions which mimic certain features of vitamin D deficiency (the various forms of resistant rickets and osteomalacia, and of renal-tubular rickets and osteomalacia).
- d. steatorrhœa, whether idiopathic or following disease, or resection of small bowel, or of stomach.
- e. renal-glomerular failure.
- f. old age.
- g. excessive phytic acid in diet.
- h. biliary obstruction.
- i. pancreatic insufficiency.

(3) Equilibrium C+D is moved over to the right—i.e. there is a gross movement of calcium from plasma to bone by—
- a. growth.
- b. heavy activity.
- c. various hormonal influences, especially too little circulating parathyroid hormone.
- d. acute pancreatitis (not proven).
- e. various bone diseases of unknown cause—e.g. marble bones disease.

(4) Equilibrium C+D is moved over to the left—i.e. bone salt dissolves into the body fluids by—
- a. old age.
- b. immobilization.
- c. large doses of vitamin D (this action is antagonized by cortisone).
- d. excessive circulating parathyroid hormone.
- e. excessive thyroid activity.
- f. active bone dissolution by tumour.
- g. various bone diseases of unknown cause—e.g. Paget's disease.

(5) Equilibrium C+D is also affected in a very controversial manner by—
- a. small doses of vitamin D.
- b. changes in acid-base balance.
- c. renal-glomerular failure.

(6) Excretion E of calcium from the plasma into the urine is increased by—
- a. any cause of hypercalcæmia.
- b. any factor which lowers the renal threshold for calcium—e.g. more vitamin D, thyroid hormone, acidosis, immobilization, osteoporosis of any origin (the vitamin D action is antagonized by cortisone).
- c. various synthetic calcium-complexing agents.

(7) Excretion E of calcium from the plasma into the urine is decreased by—
- a. any cause of hypocalcæmia.
- b. factors raising the renal threshold for calcium—e.g. vitamin D deficiency, hereditary conditions which mimic vitamin D deficiency.
- c. steatorrhœa.
- d. renal-glomerular failure.

N.B.—Remember that a shift of a dynamic equilibrium in a particular direction can always be explained in either or both of two ways, namely because of an increased movement in that direction, or because of a decreased movement away from it. Consideration of the particular factor involved has been avoided because of its complexity.

With regard to the question of phosphorus metabolism, this is in some ways similar to calcium: for instance the two are both directly concerned with the formation of bone salt. However, the main features concerned in maintaining plasma levels require in the case of inorganic phosphate to be quite differently stressed. They will be dealt with more briefly since the clinical applications are not so great as in the case of calcium. The main difference

in the case of phosphorus is that only about half of the total body store is present in the skeleton; the rest comprises a mixture of complicated but most important tissue phosphate esters and other compounds. Hence a change in phosphorus balance cannot be interpreted, as in the case of calcium, as being necessarily due to a change in the amount of bone present in the body. Another difference is that acute changes at least, in plasma phosphorus levels over a wide range (e.g. 0·5–16 mg./100 ml.) do not appear to produce in themselves any symptoms or disease. Also the main problem with calcium metabolism—namely poor absorption from the gut with a continuous threat of calcium deficiency—does not occur in the case of phosphorus since the supply and absorption is nearly always far in excess of requirement, the extra phosphorus being thrown away by excretion into the urine. Hence the problems of phosphorus metabolism and transport are better summarized in a very different form of diagram. This has been attempted in Fig. 2. The representation by means of a funnel and an overflowing tank is intended to suggest the large supply of extra phosphorus which is normally discarded, and the fact that if this supply is turned off the mechanism for retaining phosphorus is good. In other words, the kidney has a fairly sharp threshold for it and the plasma levels do not change greatly with varying intake. Chronic changes in plasma level of phosphate therefore mainly reflect changes in renal function rather than changes in supply. However, acute changes may also occur owing to a sudden disturbance of equilibrium between the large body store of phosphorus and the relatively small extracellular stores. These various factors mean that the plasma phosphate level is much more variable than the calcium level and that small changes in phosphate are not so significant unless the conditions for taking blood have been carefully standardized. A summary of the commoner clinical conditions associated with altered levels of plasma phosphorus levels is shown in Table II.

TABLE II.—FACTORS WHICH INFLUENCE PLASMA INORGANIC PHOSPHORUS LEVELS

(1) Acute rise can result from sudden liberation of phosphorus from body stores into the extracellular fluid: for instance, in starvation or surgical shock.

(2) Acute fall can result from a sudden removal of P from extracellular to intracellular compartments of the body: for instance, as the result of the increased metabolism after a heavy carbohydrate meal, or increased metabolism due to an attack of fever.

(3) Acute changes in either direction may occur for mysterious reasons in a rhythmic fashion throughout the twenty-four hours.

(4) Chronic rise in plasma P can result from raised renal threshold due to—
- a. hypoparathyroidism.
- b. excessive growth hormone activity as in infancy and acromegaly.
- c. severe renal-glomerular failure (this is mainly due to the fall in GFR).

(5) Chronic fall in plasma P can result from lowered renal threshold due to—
- a. hyperparathyroidism.
- b. vitamin D deficiency.
- c. the various hereditary (and more rarely acquired) forms of rickets and osteomalacia which mimic some features of vitamin D deficiency.
- d. steatorrhœa.
- e. rare forms of renal failure which involve renal-tubular rather than renal-glomerular dysfunction.

N.B.—When renal function is normal, ordinary changes of the P content of the diet do not have much effect on plasma P levels.

I shall now review a few clinical situations which concern disorders of calcium and phosphorus metabolism. Even if one is limiting oneself mainly to surgical matters it would be possible to spend quite a long time on any single detail. For instance, the problem of calcium absorption from the gut is of very great importance in matters concerning small-gut resection and gastrectomy. This problem has been insufficiently studied. It seems in some cases as if a condition indistinguishable from idiopathic steatorrhœa ensues with the corresponding bone disease, osteomalacia. Mr. Pyrah has shown me his own records of a case where osteomalacia appears to have followed steatorrhœa after partial gastrectomy. In other cases of ours, however, osteoporosis seems to be the result. Osteomalacia following operation for uretero-sigmoidostomy is now a well-described syndrome. One of the reasons for the lack of interest is that bone diseases nearly always take a very long time to develop, and it may be ten years or so before clinical signs of this can appear in their own right as the main complaint of the patient. They appear to be, and are, of less importance than the condition originally requiring surgery.

Disorders of plasma calcium level are, however, of immediate interest in several surgical situations. The level usually falls, for instance, in acute pancreatitis, in one case to tetany levels (Turner-Warwick, 1956). As far as I am aware this problem has not yet been studied from its metabolic aspects. Temporary, and less often permanent, hypoparathyroid tetany is well known as a consequence of neck operations. More commonly, however, the opposite

complication of hypercalcæmia occurs; as for instance after sudden immobilization of bones (plaster casts, poliomyelitis, &c.), especially in young people, and after adrenalectomy. Likewise there is an increasing awareness of the fact that hypercalcæmia may complicate primary and secondary bone tumours, especially if sex hormones are administered. The special importance of this hypercalcæmia is that it may be severe enough to cause death: more often, however, the symptoms may be very severe but self-limiting. The nausea, anorexia, lassitude and so on will certainly not be recognized as such unless one is looking for them. Disturbances of calcium excretion in the urine are of great importance in the pathogenesis of renal stone formation. [Mr. Pyrah will deal with this subject.]

The other factor shown on Fig. 1 is primary disturbances of bone formation. These often occur with very severe symptoms, presenting with a most varied and confusing symptomatology but with general health well maintained. Such patients are almost certain to be seen first by the surgeon, and it is the main point of this paper to see how it may be possible to distinguish patients with metabolic bone diseases from the other more purely orthopædic conditions. The sorting out is exceedingly difficult; the subsequent medical investigations, diagnosis and treatment are relatively easy.

Dwarfism.—I am hesitant to suggest that this obvious feature should be more often remarked upon. However, I have recently seen several adult patients of total stature around 4 ft. 7 in., in whom their dwarfism was indeed the most important physical sign leading to the eventual diagnosis, but which had not been remarked upon previously. Moreover, hospital records (even in pædiatric and orthopædic departments) often include no details of height. I think that any case in which the expected height is 10 in. or so below normal should be considered as a possible case of bone disease until proved otherwise.

Apart from looking for obvious deformities which might have caused the dwarfism it is important to determine the body proportions to see if these are abnormal. A relatively short trunk suggests recent softening of vertebræ, especially if there is a history of loss of height or if the height is less than the span. On the other hand, relatively short legs suggest a disorder of the growing ends of the bones such as rickets or the various diseases like it. If the dwarfed patient is well proportioned and without deformity then the bone disease, if present at all, is likely to be very mild and of long duration. Certain forms of mild renal disease show in this way, as also any lifelong steatorrhœa, which is not also complicated by the more gross bone changes of osteomalacia. It is also necessary to consider all the endocrine glands. However, if these are grossly disordered the patient is likely also to have other presenting symptoms and signs which usually means that he is likely to go to a physician rather than to a surgeon.

The question of dwarfism in childhood is often a rather difficult one to be sure of in view of the great variation of growth rates. Even here, however, stature should always be plotted in doubtful cases on charts showing the normal range of variation, and also previous records of height so that this too can be plotted. Change in rate of growth is of far more significance than a constant slowed rate of growth. Almost any chronic infective or metabolic disease of childhood, if sufficiently long-lasting, will show as a slowing of the growth rate. Likewise the keeping of proper records of subsequent growth is the best measure of the adequacy of one's treatment, far better than biochemical methods of control which reflect only the immediate condition.

Pathological fractures.—These are exceedingly difficult to interpret if they appear to have occurred without undue trauma in otherwise normal-looking bone. We do not manage to explain the majority of these on a metabolic basis, especially if the fractures are complete and heal well. Such apparently brittle bones are occasionally due to the late presenting form of osteogenesis imperfecta, a condition which is not always very serious. Apart from the well-known sign of blue sclerotics, there is the important sign of loose ligaments such as undue mobility of the knee-joint, flat feet, dislocation, &c. If patients are over 30 years of age the presence of a high-tone deafness can sometimes be measured and is of some help: the patient may not for some years notice any change of hearing.

Incomplete fractures which are slow in healing present the problem as to whether these are fatigue fractures in normal bone, or are signs of more generalized bone disease such as the Looser zones of osteomalacia. These may be impossible to distinguish on the X-ray but fortunately we have good biochemical diagnostic measures to help us (*see* later).

Pathological fractures of the ribs and pelvis with excessive callus formation may be due to Cushing's syndrome whereas repeated rib fractures without callus formation and which heal fairly well are often the main complaint in idiopathic and senile osteoporosis. We are interested at the moment in the problem of fragile bones occurring in chronic liver disease and have collected data from a few cases where this was the presenting sign, the liver disease being inconspicuous at first. We have nothing to contribute on the treatment of this condition. Another unusual cause of fragile bones in adults is the rare syndrome of hypophosphatasia, of which we have had one example recently, and have had details of a further

case kindly sent to us by Dr. P. Henneman (Boston, U.S.A.). A clear case of this interesting adult syndrome was reported briefly by Macey (1940). All the other cases so far have been in the pædiatric literature (Rathbun, 1948; Sobel *et al.*, 1953). In children the disease has some resemblance to rickets.

Vaguely localized pain.—Nearly all our patients with bone disease have had pains of varying severity in different parts of their bodies, and if this is the only manifestation it is impossible until something else happens to diagnose such a case. We have even noted patients who were at first symptom-free but who had biochemical abnormalities pointing to osteomalacia. Even knowing this, the odd aches and pains from which they later suffered were not particularly characteristic and during their follow-up we were not convinced that they were due to the impending bone disease until we had seen them get worse and then at last treated them and noted the remarkable response to treatment.

In children the pains are almost entirely limited to the legs. In an adult, however, with generalized bone disease the commonest site for pain is in the lower back. After this it is probably most common in the hips and thighs, and in such cases it is usually bilateral and not located to the backs of the thighs but rather vaguely down the middle of the legs. After this come tenderness in the ribs and pains in the feet. If the pains are fairly generalized the ribs in particular are likely to be tender to touch. The only simple clinical investigation that is worth doing on everybody about whom one is suspicious is to measure their body proportions since the crown-to-pubis measurement in such cases due to bone disease is almost certainly 2 in. or more shorter than from pubis-to-heel. Further investigations would then be justified if this is found. Most of our patients before reaching us have been variously diagnosed and treated for slipped intervertebral disc, arthritis, tuberculous hip, or ankylosing spondylitis, and, of course, psychoneurosis.

As nearly all of the bone diseases that present in this way are progressive some further physical signs are likely to appear before long that would make correct diagnosis more easy. In some cases, however, this has not been achieved till after symptoms had been present for as much as ten years, but in these it has always been possible in retrospect to discover some physical signs—such as a loss of stature, a Looser zone on an X-ray, a complaint of muscular weakness or a gait abnormality—which had appeared much earlier but had been ignored.

Muscular weakness.—It is a very curious feature, hardly stressed in the literature, that there is nearly always a varying degree of muscular weakness present with metabolic bone disease, especially osteomalacia. At times this may not be apparent on examination and may only take the form of a complaint by the patient that he is too easily tired or feels a weakness in his thighs which makes it difficult for him to go upstairs. In other cases this may be much more generalized and readily apparent as a gross hypotonia. We have known rarer cases when the weakness was so severe that the patient could only lie on his back; complete raising of arms and legs off the bed was impossible and even the head, could not be raised off the pillow. Often this weakness is associated with the more severe forms of osteomalacia when bone pain is conspicuous and it is easy to imagine that it is a reflex due to the increased pain which comes on movement. This, however, is probably not the correct explanation since the degree of muscular weakness does not appear to be related at all closely to the amount of pain. In one or two cases excessive weakness in the absence of pain had led to a first diagnosis of muscular dystrophy. The muscular weakness disappears as if by magic when the osteomalacia is adequately treated.

Muscular weakness and hypotonia is a well-known concomitant of hyperparathyroidism. In these cases presumably it is due to the hypercalcæmia since it is common to hypercalcæmia of any origin.

Gait abnormality.—The only important one of these is the waddling gait which is exactly the same as may occur in many surgical diseases. It may be associated with a coxa vara of the hip in a case of osteomalacia, but that it is not due to this entirely can be readily seen, for it often disappears largely on treatment and may sometimes appear as the first sign, before any radiologically detectable bone deformities have occurred. It may also occur without any pain, and in one of our patients, whom we had under close observation as we thought for biochemical reasons (there were no signs or symptoms) that he was probably in course of developing an osteomalacia, the waddling gait appeared—and was soon very marked—three months before any other manifestations, radiological or symptomatic. This waddling gait disappears rapidly in such cases when the patient is treated, and we presume that it is a manifestation of muscular weakness of the glutei muscles.

These patients may also have difficulty in rising from the sitting position just as in a case of muscular dystrophy. They may also complain of a feeling of stiffness around the hips and other joints which is much worse after they have been resting for some time but works off a little on moving about. This situation was well noted by Milkman (1930) in his first description of the syndrome often known by his name.

Osteoclastomata.—These have been often stressed as being the presenting signs in some cases of hyperparathyroidism. They most frequently occur in the jaw, but may in fact occur almost anywhere. Clearly, however, every such case should be considered as being possibly due to hyperparathyroidism before undertaking any drastic surgical treatment. I have been unable to find figures for the proportion of these, especially of the jaw tumours, which are due to hyperparathyroidism, and the proportion of unknown origin. There is a revealing statement in Thoma (1944), where it states of a patient with an osteoclastoma in his jaw "the blood chemistry was normal, Calcium 11·5 mg./100 ml., Phosphorus 1·9 ml./100 ml., Phosphatase 1 Bodansky unit".

Slipped epiphyses.—Renal rickets presenting as bilateral slipped epiphyses of the femoral heads is well described in the literature, and I have records of one such case. This should not be difficult to distinguish from other causes producing the same radiological appearance since the patient is almost certain to be dwarfed and to have proteinuria. Other signs of renal failure will be found on further investigation.

Decayed teeth.—In hypophosphatasia a gross disorder of tooth formation occurs. The milk teeth decay and drop out prematurely, likewise the permanent teeth cause a great deal of trouble and are likely to have been extracted or lost by the early twenties. Unfortunately in the present state of our ignorance this is the only metabolic bone disease in which the study of the teeth is of great help in diagnosis. Decayed teeth, late to erupt and with poor root development, occur in chronic hypoparathyroidism, but this is not strictly a bone disease.

Heredity.—It is of great help in diagnosis if a patient with suspected bone disease has a close relative similarly affected, since very many of these diseases are now known to run in families according to known rules of inheritance. The hereditary forms of rickets and osteomalacia have been reviewed (Dent and Harris, 1956). A disease can still be hereditary even if it does not present with clinical signs till later in life; it need not be there from birth. The fact that a disease is hereditary is irrelevant to the question of treatment as there is excellent treatment for some hereditary diseases.

Renal pain and other symptoms.—Renal colic, with or without demonstrable stone but associated with, and indeed caused by, a hypercalciuria, is commonly the presenting sign in any rapidly progressive form of bone disease. The calcium lost from bone by any process of bone dissolution (neoplastic or metabolic) is mainly excreted into the urine. The urine calcium output, which is readily determined, may be a good measure of the rate of bone

TABLE III.—BIOCHEMICAL CHANGES IN SOME METABOLIC BONE DISEASES
(Modified from Dent and Hodson, 1954)

	Plasma Ca (mg./100 ml.)	Plasma P (mg./100 ml.)	Plasma HCO_3 (m.Eq./l)	Blood urea (mg./100 ml.)	Alkaline phosphatase (K–A units)	Urine Ca (mg./24 hr.)
Normal (adult)	9–11	3–4	24–28	20–35	5–12	120–220
Idiopathic osteoporosis	.....	.....	NORMAL	.....	.....	(high if in an active phase)
Primary hyperparathyroidism	11–16§	1–3§	normal§	normal§	15–100*	300–800§
Chronic renal failure / Renal-glomerular osteodystrophy / Secondary hyperparathyroidism	6–11	4–12	10–22	50–400	15–100	50–200
Rickets or osteomalacia,† any origin, non-acidotic	8–10	1–3	20–28‡	normal	5–50	10–100
Rickets or osteomalacia,† acidotic	7–11	1–4	10–22	30–80	15–50	150–350
Hypophosphatasia	9–15	4–8	20–28	20–100	1–2 (adult) 3–8 (infant)	Insufficient data, probably high normal or high

*The phosphatase is normal in those cases of primary hyperparathyroidism in which no generalized bone changes occur.

†Some of these cases are also associated with other signs of renal tubule dysfunction such as renal glycosuria, renal aminoaciduria, hyperpotassuria and pitressin-resistant diabetes insipidus. The acidotic cases also show defective urinary acidification and often defective ammonia formation.

‡Note that occasionally low bicarbonate levels occur in cases which have no acidosis as measured by urine Ca output or other means. We are investigating this curious phenomenon.

§If renal failure occurs these figures will approach those characteristic of secondary hyperparathyroidism.

dissolution and changes in it may therefore be a measure of the efficacy of treatment. Note, however, from Table I the various other causes of hypercalciuria (and of consequent stone formation).

Instead of the symptoms due to stone or gravel formation, the patient may complain of symptoms due to the chronic renal damage resulting from a long-standing hypercalciuria—thirst, polyuria, nocturia, &c. In cases of very rapid bone dissolution a marked hypercalcæmia may develop and produce its own symptomatology—anorexia, lassitude in milder cases, with vomiting, abdominal pain, thirst and dysuria if more severe.

Preliminary sorting methods for patients suspected on clinical grounds of having metabolic bone diseases.—Fortunately, once a metabolic abnormality has been detected the further investigation and diagnosis is relatively easy, even if rather time-consuming. One needs, however, a further battery of routine tests to apply to any patient who is under suspicion on clinical grounds. Here radiology becomes of great importance. This has been briefly reviewed already (Dent and Hodson, 1954). If the X-rays uphold the suspicion then the biochemical determinations must be done, as shown in Table III. A provisional diagnosis can then be made which can be checked by further appropriate investigations and a final review of the clinical data [*see also* Albright and Reifenstein (1948) and some reviews].

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Mr. L. N. Pyrah (Department of Urology, University of Leeds, Leeds General Infirmary and St. James' Hospital, Leeds) [*Abridged*]:

In this paper I shall consider some of the conditions in which calcium salts (the commonest constituent of urinary calculi and of intra-renal calcific deposits) are deposited in the renal parenchyma and the renal passages. In two-thirds of all the calcium-containing stones we do not understand the cause; in one-third of such calculi and in most cases of nephrocalcinosis we know something of the mechanisms of their causation.

We found that if normal kidneys were microscoped after autopsy in patients in whom there had been no intrinsic renal disease nor any metabolic cause of renal calcification, small calcific foci were present in 21% of 103 pairs of kidneys examined; these small foci were found almost exclusively round the upper collecting tubules or within the tubular lumina and they probably represent past minor pathological incidents of a vascular or infective character.

Urinary calcium output.—We have compared the range of calcium excreted in twenty-four hours in the urine, in 162 patients having renal calculi, and taking a normal diet, with the same number of non-calculous patients also on a normal diet (Fig. 1). The normal range of urinary calcium varies widely; comparison of the two groups of patients shows that the calcium excretion of patients with renal stone covers a wider range than that in normal people. Some patients with renal calculus had a high urinary output of calcium and some had a low output. 13 patients in the group had a urinary calcium output below 50 mg. per twenty-four hours; 7 of these 13 patients had only one kidney which was functioning; 2 had bilateral hydronephrosis and 4 had relatively normal function. The findings suggest that the low urinary calcium is often the result of poor renal function, the calcium not being filtered in normal amounts through the glomeruli. It is possible that in some of these cases with bad renal function, because of the low urinary calcium content, the stone-forming process comes to an end. If calculi are removed in cases with very bad renal function, recurrence does not necessarily take place, even when on other grounds it might be expected to do so (Pyrah and Raper, 1955).

We regard 350 mg. of calcium per twenty-four hours (the patient being on an ordinary

diet), as the upper limit of normal and patients having higher values than this are given a low calcium diet (150 to 200 mg. calcium daily) for six days for special study, twenty-four-hour specimens of urine being collected for urine calcium estimations during the last three days; on this regime in some cases the urinary calcium remains high, in others it falls to normal. Within this group, patients have been found with adenoma of the parathyroid and also cases of renal acidosis with nephrocalcinosis or stone, but it is still not possible to classify some of them; for the present we regard them as cases of idiopathic hypercalciuria.

Recumbency stones.—During enforced recumbency for the treatment of fractured spine or pelvis, tuberculosis of the spine or hip and other conditions, it has been shown that there is a greatly increased output of calcium into the urine, which is probably temporary. The more complete the immobilization, the greater the amount of calcium excretion; a peak in the output curve of calcium is reached in four to five weeks during simple recumbency but in one to two weeks when there is a fracture. The serum calcium rises very slightly or not at all, except in children and in patients with Paget's disease. If in such patients the urine becomes highly concentrated and alkaline in reaction, calcium phosphate may be precipitated in the renal calyces and since, in the recumbent patient the urinary stream flows upwards from the renal calyces and pelvis (which are low) to the bladder, as illustrated by a lateral pyelogram (Fig. 2), crystalline material may clump together to produce the simplest

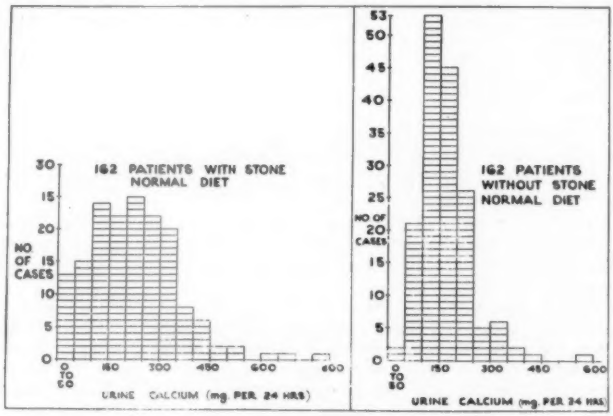

FIG. 1.—Average urinary calcium output of 162 patients with renal stone compared with a group of 162 patients with normal kidneys.

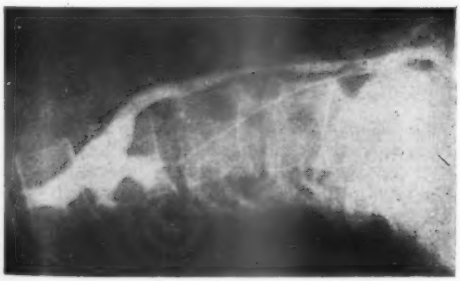

FIG. 2.—Lateral pyelogram taken with the patient recumbent; this shows the dependent position of the calyces and upward direction of the ureter from the renal pelvis to the brim of the bony pelvis.

type of recumbency stone, namely the so-called mud stone of pure calcium phosphate. If there is an associated urinary infection, as often occurs in women, the more solid mixed phosphate and oxalate calculus bound together by colloid may be formed. While the recumbency stone still consists of a muddy mass of pure calcium phosphate, if the patient is turned frequently, given massage and movement to unsplinted limbs, and given abundant fluids and also a mixed diet to ensure that the urine has a slightly acid reaction, the stones may disintegrate and disappear; mobilization arrests the calcium loss and the stones do not recur. Recumbency calculi are still common, having accounted for 30 of 600 cases in our departmental series of renal calculi; with careful treatment they should be largely prevented.

Primary hyperparathyroidism.—In primary hyperparathyroidism, due to adenoma, diffuse hyperplasia or carcinoma of the parathyroid gland, the direct clinical results of the disturbed calcium metabolism, are seen in the decalcification and other changes in the bony skeleton and in the calculosis and nephrosclerosis of the kidneys; and these two groups of changes may occur separately or together.

Although first recognized as a skeletal disease, sometimes with accompanying renal calculi, it is now known that cases having skeletal changes alone are the least common and cases having renal calculi alone are the most common manifestation of hyperparathyroidism; this change of emphasis in examples of this disease discovered by clinicians has been especially noticed in cases published in the last eight years. In a review of all cases published in the world literature by Norris to 1947, 314 cases in all, 191 cases had skeletal changes alone, 101 had skeletal changes with renal calculi or nephrocalcinosis and in only 17 cases had hyperparathyroidism been recognized with renal stones as its sole clinical manifestation, skeletal changes being absent. By contrast, series of cases published since 1947 (Table I)

TABLE I.—SERIES OF CASES OF PRIMARY HYPERPARATHYROIDISM PUBLISHED AFTER 1947

Type	Albright and Reifenstein 1948	Burk 1948	Lahey and Murphy 1953	Richardson 1953	Black 1953	Hellstrom 1954	Total
Skeletal changes alone	11	3	16	—	16	13	59
Skeletal changes with nephrocalcinosis or renal calculi	24	7	9	7	16	10	66 (±7)
Nephrocalcinosis or renal calculi alone	28		4	4	73	27	136 (±7)
Neither skeletal changes nor calculi	1	—	—	—	7	—	8
Total	64	10	29	11	112	50	266

show that a growing proportion (in some series more than half) have been diagnosed because of renal stones alone, skeletal changes being absent; these cases have been diagnosed by careful biochemical screening of cases of calcium-containing renal calculi or of nephrocalcinosis attending urological clinics.

Our own series in Leeds has consisted of 35 cases of hyperparathyroidism seen over a period of twenty-one years; 4 of these cases were autopsy cases and were not operated on because they reached hospital very late or *in extremis*, while 31 cases were operated on; the proportion of cases in the series having skeletal changes, calculi and nephrocalcinosis is shown in Table II. In the last two years 16 cases of hyperparathyroidism have been operated on and of these 12 had renal calculi, 8 with no skeletal changes (Table II).

TABLE II.—PRIMARY HYPERPARATHYROIDISM—LEEDS SERIES 1934–55

35 cases	Skeletal changes alone	13
	Skeletal changes + renal calculi or nephrocalcinosis	14
	Renal calculi or nephrocalcinosis alone	8
	Operation cases in last 2 years	
16 cases	Skeletal alone	4
	Skeletal + calculi	4
	Renal calculi alone	8

The renal changes in hyperparathyroidism most easily recognized are calculus formation and nephrocalcinosis. In cases with skeletal changes soft, often bilateral, phosphatic calculi may be deposited as a cast of the renal pelvis and/or of some of the calyces, and these may disappear within a few weeks of the removal of the parathyroid adenoma, if the patient is mobilized and given copious fluids, a mixed diet and ammonium chloride, to render the urine slightly acid. Another example of calcification is diffuse nephrocalcinosis (Fig. 3) which occurs in the renal pyramids and later in the medulla; in the early stages the radiograph may show the kidneys stippled with fine calcific deposits widely dispersed through the renal parenchyma or as a cluster of tiny calculi round one or more calyces. Nephrocalcinosis does not in my experience disappear after the removal of the parathyroid adenoma, the renal changes probably being irreparable. Most deceptive for the surgeon and indeed the ones which are still being missed, are the renal calculi in the hyperparathyroid patient which do not differ radiologically from the common idiopathic calyceal stone (Fig. 4).

Recurrence of the renal stone after operative removal must be expected in cases of hyperparathyroidism if the adenoma is not dealt with. The other more insidious change in the kidney resulting from the hypercalcæmia and the hypercalciuria is the nephrosclerosis accompanied by a lesser or greater degree of microscopic parenchymal calcification through-

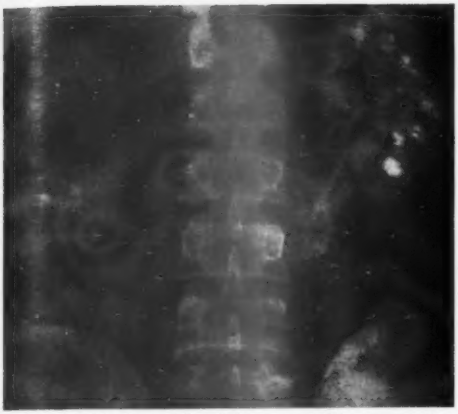

FIG. 3.—Nephrocalcinosis in a case of hyperparathyroidism; the only bony change was a cyst of the lower jaw.

FIG. 4.—Solitary stone in pelvis and lowest calyx; the right kidney had been previously removed for calculi; the patient had no skeletal changes but a parathyroid adenoma was subsequently removed.

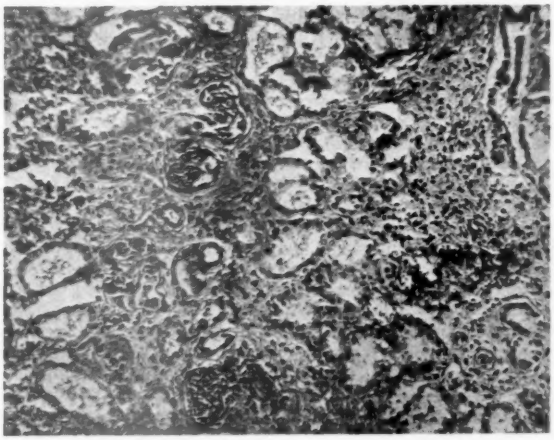

FIG. 5.—Calcification and sclerosis in the kidney of a patient with hyperparathyroidism.

out the kidney (Fig. 5), and this is not necessarily corrected after the adenoma has been removed. There may be widespread destruction of individual nephrons with deposition of calcium salts in the cells of the renal tubules, later the cell bodies may be destroyed and extruded into the tubular lumen, with the formation of calcium casts. Following on these widespread changes, clinical hypertension may develop and has been found in a number of my cases. The 4 cases in my series admitted to hospital *in extremis* were known to have suffered from hypertension and, in fact, died from uræmia or anuria. The patient with a renal stone resulting from a parathyroid adenoma, has less chance of normal health and even of survival than has the patient with the idiopathic renal stone; it is important therefore that a possible diagnosis of hyperparathyroidism should be considered in every case of calcium-containing renal stone.

The diagnosis of most of the cases of hyperparathyroidism in the series, especially those with skeletal changes, has been comparatively easy and at operation the tumour in the neck has been sufficiently large to make its discovery at operation not difficult. In cases having renal stones alone not only may the diagnosis be difficult, because we are often dealing with small deviations from the normal levels of serum calcium and plasma phosphorus, but the tumour in the neck may be very small, necessitating a long search at operation, moreover the tumour may lie deep in the anterior mediastinum.

The serum calcium level is the most important single biochemical examination. Consistently high readings of 12 to 17 mg.% will make the diagnosis easy; such high levels in my series have usually occurred in cases having skeletal changes with or without renal stones. In some cases with renal stones alone, the serum calcium levels may lie between 11 and 12 mg.%. The biochemist who carries out the examination must be able to achieve results which are not only consistent but of such accuracy that readings of serum calcium above the top normal figure for his laboratory (in our case 11·0 mg.%) must be suspect. Repeated readings on different days exceeding 11·0 mg.% are then very suggestive of hyperparathyroidism. In Black's series (1953) of 112 cases of hyperparathyroidism, he reported 8 of 108 cases with serum calcium levels of 10·5 to 10·9 mg.% and 56 of 108 cases with serum calcium levels of 10·5 to 12·4 mg.%, the top normal reading for his laboratory is 10·6 mg.%. If kidney function is reasonably good, as indicated by a normal blood urea examination, the normal plasma phosphorus is 3·5 to 5 mg.%. A plasma phosphorus between 1·5 and 3·5 mg.% when taken in conjunction with a raised serum calcium, is suggestive of hyperparathyroidism. The serum alkaline phosphatase is high in skeletal cases and normal in cases having renal stones alone; if it is slightly raised a careful radiological examination of the bony skeleton must be made and the three sites to be first examined are the skull, which may show a ground-glass appearance from early decalcification, the middle phalanges which may show the lace-like pattern due to subperiosteal resorption and the tooth sockets which may show an absent lamina dura.

The patient is then given a low calcium diet of 125 to 150 mg. of calcium daily for six days and the urinary calcium is estimated during the last three days of this period. A daily average output of less than 150 mg. of calcium is normal, 150 to 200 mg. is suspicious of hyperparathyroidism and 200 mg. or more strongly supports such a diagnosis. Impaired renal function as judged by a lack of concentrating power and a consequent low specific gravity of the urine using the water concentration test, supports along with the other factors mentioned, a diagnosis of hyperparathyroidism; the blood urea may be raised.

Gastric conditions.—Patients having peptic ulceration of the stomach or duodenum may suffer from renal damage with calcification either resulting from complications of their ulcer or because of errors in treatment.

Consequent upon severe pyloric stenosis with intractable vomiting, followed by hypochlorædmic alkalosis and death in coma, the kidneys usually show well-marked tubular degeneration and calcification, usually in the distal convoluted tubules and the loop of Henle, and there may be calcified intra-tubular casts; this form of renal calcification is partly dystrophic and partly on account of the alkalosis which favours the precipitation of calcium phosphate. Excessive and prolonged doses of alkali, such as were often given in the Sippy regime, may cause temporary impairment of renal function with drowsiness or coma; in the few fatal cases reported, the kidneys have sometimes shown tubular changes including calcification. In milk-drinker's syndrome, the high intake of milk, often amounting to two or three quarts a day especially when taken together with alkalis to relieve ulcer pain, may produce gross nephrocalcinosis with renal failure and hypercalcæmia without hypercalciuria; the plasma phosphorus may be normal or high. Widespread calcification may develop in the subcutaneous tissues, especially around the joints and in the pulp of the fingers.

If the renal calcification which occurs in the above gastric conditions or during the course of their treatment has anything to do with stone formation, it may be expected that patients with peptic ulcer would have a higher incidence of renal calculi than normal individuals. A group of patients with stone and a group of patients with ulcer have been questioned and there is evidence to suggest that there is a relationship between the two conditions (Table III).

TABLE III.—AN ANALYSIS OF PATIENTS WITH PEPTIC ULCER AND RENAL STONE WHICH SUGGESTS THAT THERE IS A CONNEXION BETWEEN THE TWO CONDITIONS

(A)	1953–54 Admissions 38,939	Ulcer 1,383 (3·55%)	Stone 149 (0·38%)
(B)	495 ulcer patients questioned		
	Expected No. with stone (0·38%)	= 2	
	Actual No. with stone	= 8	
(C)	308 stone patients questioned		
	Expected No. with ulcer (3·55%)	= 11	
	Actual No. with ulcer	= 32	

Acknowledgment.—I desire to thank Mr. M. C. Oldfield for permission to reproduce Fig. 3.

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Mr. H. Hamilton Stewart (Urological Department, Bradford Royal Infirmary) [*Précis*]:

The following observations were made following the performance of 152 operations of partial nephrectomy carried out over a period of sixteen years on 144 patients suffering from primary renal stone (Stewart, 1952, 1953, 1955). Infected and non-infected cases were included. 139 of the kidneys operated upon were X-rayed in a follow-up examination; the remaining cases could not be traced or had died from other causes. There was a recurrence rate of 7·9% but in my opinion this figure could be considerably reduced now that I know more about the basic principles involved in the treatment of renal stone.

The majority of renal calculi form in the lower pole of a kidney—73% in the lower pole alone. If several segments are stone-forming, then in over 80% of these kidneys stones are formed in the lower pole as well as in other parts.

In over 25% of the cases the kidneys operated upon had formed stones repeatedly prior to the operation and 5 out of the 11 recurrent cases recorded came from this group. Males suffer from primary renal stone more frequently than females—96% as against 56%.

A study of the recurrent cases revealed that in all but one the recurrence was in the lower pole and was located in a minor calyx or in the truncated major calyx which had not been removed at the time of the partial nephrectomy. It thus appears that if a recurrence of a primary calculus is to be prevented then the major calyx with all its associated minor calyces must be removed in a lower polar partial nephrectomy, a segmental resection thus being performed. The removal of a minor calyx alone is insufficient to prevent recurrence. In the upper pole the risk of recurrence after removal of a minor calyx alone is much less than in the lower pole. If conservation of renal tissue is essential then an incomplete upper polar partial nephrectomy (calycectomy) is justifiable.

The lymphatic theory of origin of renal stone expounded by my colleague Dr. Carr of Bradford (Carr, 1954) explained facts which I have observed by practical experience and in the follow-up of cases.

Suggested Classification of Renal Stone

A. *Primary stones.*—These stones originate in the renal cortex. It is wise at this stage of our knowledge to classify primary stones from the ætiological point of view into two groups. It is not unlikely that the fundamental explanation of both groups may lie in the lymphatic theory of causation:

(i) Randall's stones—these form on calcified plaques on renal papillæ.

(ii) Carr's stones—stones with one or more nuclei; these nuclei are calcium concretions which collect in forniceal pouches and may form one large stone or multiple small ones. Occurrence of these stones which may have multiple spherical bodies as a nucleus has been confirmed by Prien (1955) who concurs that Randall's theory (1937) cannot explain them.

The origin of both types of primary stone is in the renal tissue. They form on a segmental or, in the upper pole, possibly on a partial segmental basis. If a metabolic disease is present, then usually all segments are involved and the disease tends to be bilateral.

B. *Secondary stones.*—These stones originate initially in the pelvi-calyceal system itself, and are associated with infection, stasis, obstruction (which may be due to a primary stone), recumbency, or vitamin deficiency.

Treatment of primary renal stone.—The presence of a primary stone in the urinary tract is a symptom of a disease and removal of the calculus alone may therefore be insufficient to cure the patient and prevent recurrence. In a small percentage of cases the disease may be one of metabolism or of the renal tubules themselves, and in these cases, although surgical treatment may be necessary to deal with emergencies, the main effort of the surgeon should be directed to a cure of the general disorders.

As a rule, however, the primary lesion is in the kidney itself, and very often only a single segment is pathological and stone-forming.

Stones in the lower pole should be treated by complete removal of the lower pole, a segmental resection being performed. If a stone is also present in the middle calyx, or "concretions" are seen in direct relationship to this calyx, then this portion of the kidney should also be removed in addition to the upper or lower pole. Stones in the upper pole should be treated by removal of all the minor calyces of the upper pole unless it is absolutely essential that the maximum amount of functioning renal tissue should be preserved, in which case the removal of the involved calyx alone is justifiable.

Treatment of primary uretero-pelvic calculi.—In addition to removal of the calculus from the uretero-pelvic system, a partial nephrectomy should be performed if clinical radiographs or X-rays of the exposed kidney revealed definite proof of their origin. The stone-forming pathological segment should be resected.

The importance of high quality X-rays and pyelograms taken of the kidney exposed at operation cannot be over-stressed. The final decision as to the best operative procedure can only be reached after a study of these X-rays.

Although stones do result from disordered calcium metabolism, I do not believe that this is the common cause. If it were, then the results of partial nephrectomy should have been very poor as the underlying cause would not have been removed by this operation, but the follow-up of cases over a period of sixteen years following partial nephrectomy has shown very satisfactory results.

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Dr. D. N. Baron (Royal Free Hospital, London):

Treatment of Acute Hypercalcæmia with a Chelating Agent

A serious complication of the treatment by androgens of malignant deposits in bone is a rapid onset of hypercalcæmia with renal failure and a high blood urea, which may occur even if the deposits themselves had not affected the serum calcium level. Until recently the only treatment available for the hypercalcæmia was cessation of the androgen therapy, when the biochemical abnormalities very slowly returned to normal.

Ethylene-diamine-tetra-acetic acid (EDTA, edetic acid) and its derivatives can be used, as chelating agents, to remove certain metals from the body, and are principally valuable in the treatment of lead poisoning. When used for the treatment of chronic hypercalcæmia (for example due to carcinomatosis or multiple myeloma) EDTA produces only a temporary remission as the cause of the hypercalcæmia persists, and hypercalcæmia returns when treatment is stopped; prolonged use of the drug may cause renal tubular damage and other toxic manifestations (Holland *et al.*, 1953; Dudley *et al.*, 1955; Spencer *et al.*, 1956). Dudley *et al.* (1955) also treated, without marked success, a case of acute hypercalcæmia due to hypervitaminosis D.

The apparently successful use of a chelating agent in the treatment of acute hypercalcæmia due to androgen therapy is shown in the following case report.

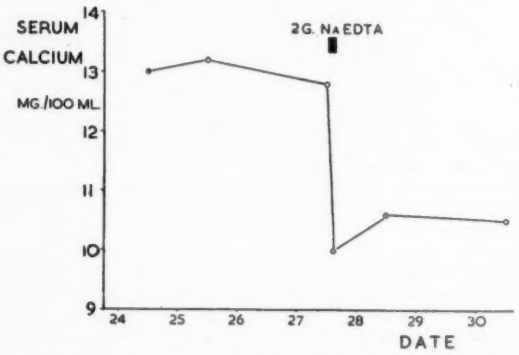

FIG. 1.—Effect of an intravenous infusion of di-sodium ethylene diamine tetra-acetate on the hypercalcaemia resulting from testosterone therapy of metastatic carcinoma of the breast. (Admitted July 24, 1955.)

Mrs. G. M., aged 42, suffering from carcinoma of the breast with multiple bony metastases, was being treated whilst at home with testosterone propionate.

She was readmitted to hospital on 24.7.55 because of nausea and vomiting, which were presumably due to hypercalcæmia (serum calcium 13·0 mg./100 ml.) resulting from the therapy—for the serum calcium was normal before testosterone was given. Testosterone therapy was stopped, but the serum calcium remained high and she retained the symptoms of hypercalcæmia. She was then treated by an intravenous infusion of 2 grams of sodium EDTA (as sodium versenate) in 500 ml. 5% glucose, administered over three hours.

The serum calcium level (measured by the oxalate precipitation method) fell immediately, as shown in Fig. 1, and stayed within normal limits for the remainder of her stay in hospital. The symptoms due to hypercalcæmia abated and did not return. Unfortunately it was not possible to perform balance studies.

I would like to thank Mr. E. J. Radley-Smith for permission to quote the clinical details, Dr. C. E. Dent for his advice, and Mr. J. W. Hadgraft for preparing the versenate solution.

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[*April* 4, 1956]

Coarctation of the Aorta Associated with an Aneurysm Leaking into the Bronchial Tree, Treated by Aortic Resection and Grafting.—W. R. PROBERT, M.Chir. (for DILLWYN THOMAS, F.R.C.S.).

W. B. C., male, aged 15½. Telephonist.

History.—Age 15. Cardiac murmur discovered at school medical examination. October 1952: Developed febrile illness with malaise, pains in back and legs and unproductive cough. December 1952: Admitted to hospital. Coarctation of aorta discovered. B.P. Right arm 180/110; left arm 180/110. Femoral pulses delayed and weak. Systolic murmur left 2nd intercostal space, neck and back. Blood culture × 3: *Strep. viridans.* Urine contained red blood cells. Chest X-ray: rib notching. W.R. negative. Endocarditis treated with penicillin for ten days then Aureomycin for three months, under the care of Dr. Ernest Evans. April 1953: Blood culture sterile.

April 17, 1953: First operation—left thoracotomy. Coarctation at usual site. Aneurysmal dilatation distally, not fully explored but deemed inoperable. Two months' more Aureomycin treatment given.

Post-operative progress.—Immediate recovery satisfactory. He remained well apart from occasional headaches though the aneurysm increased in size rapidly in the first year, and more slowly in the second year. August 1954: Started light work. October, 1955: Febrile illness with unproductive cough for three weeks.

November 28, 1955: Readmitted to hospital as an emergency after a severe hæmoptysis (150 ml.).

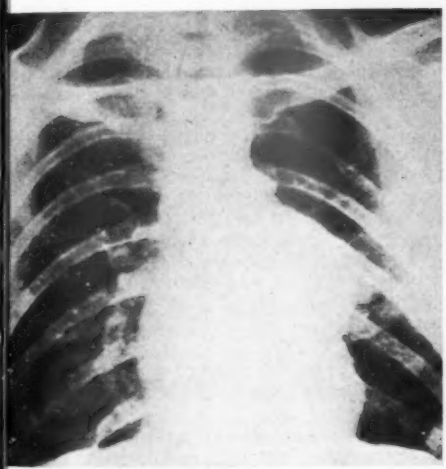

FIG. 1.—P.A. chest radiograph 20.12.55 showing prominent left subclavian artery and aneurysm distal to coarctation site. Rib notching is best seen in the right 8th rib, and the left 5th rib has regenerated following the first thoracotomy.

FIG. 2.—Left lateral tomogram of chest, 4½ in. cut, showing aneurysm intimately related to the apical segment of the left lower lobe, and changes in the basal segments.

December 20, 1955: Following X-ray examination (Figs. 1 and 2) he had a massive hæmoptysis, estimated to have been at least 1,200 ml. and collapsed. He recovered; and there was no further hæmoptysis. January 4, 1956: Second operation. Hypothermia by surface cooling to 30° C. (Professor W. W. Mushin). Left thoracotomy. Lung densely adherent over aorta. Dissection was started and intercostal vessels divided in such a way that the aorta above and below the lesion could be clamped as early as possible. Coarctation

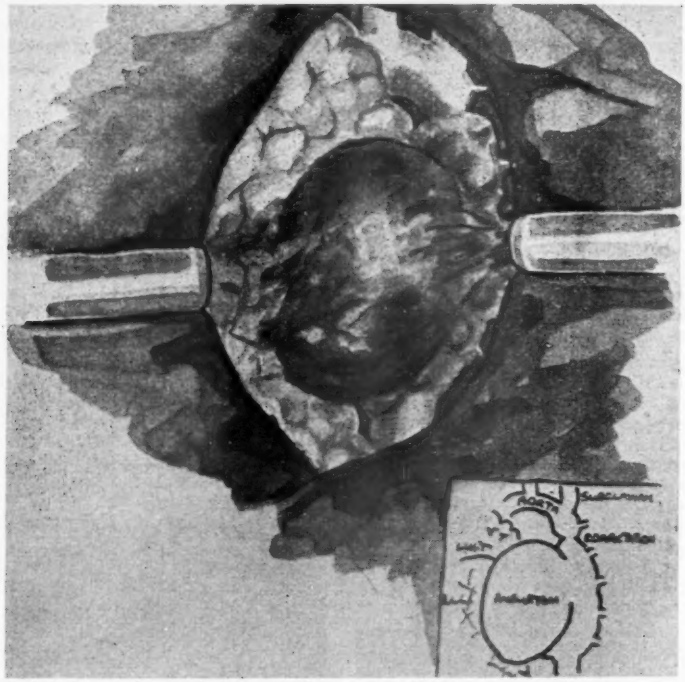

FIG. 3.—Artist's impression and diagram of operation findings. Apart from the aneurysm the irregularity of the dilated aorta distal to the coarctation is well shown.

at common site, one pair of intercostal arteries arising above it. Aorta distally very dilated and "knobbly", with non-pulsating aneurysm approximately 7 cm. in diameter lying anteriorly intimately associated with apical segment of left lower lobe (Fig. 3). Aorta clamped above coarctation (leaving left subclavian artery free) and below at level of pulmonary ligament. Six pairs of intercostal arteries ligated and divided; aneurysm freed with difficulty and drawn forward still intimately bound to lung. Aortic defect (12·5 cm.) bridged with freeze-dried homograft. Aneurysm removed piecemeal to avoid damage to pulmonary artery; thick wall with much old laminated clot trimmed away. When loose clot was removed from false aneurysm sac a fistula into a sub-segmental branch of the apical bronchus of the left lower lobe was revealed. The fistula was sutured; and aeration of left lower lobe was much improved.

Post-operative progress.—At the end of the operation, the patient regained consciousness, spoke intelligibly, moved all his limbs freely and passed urine. Rewarming took three and a half hours; convalescence uneventful thereafter.

Present state.—B.P. Right arm 180/85; left arm 180/85. Good femoral pulses; posterior tibial and dorsalis pedis pulses now palpable. Urine normal. Though he had not made any specific complaint before, he says that his feet are warmer and that he is free from pulsating sensations in the head.

Comment.—The co-existence of aneurysm and coarctation of the aorta is now well known. Following pioneer work by Swan *et al.* (1950) and Gross (1951) in America and by Sir Russell Brock (Brock and Graham, 1952) in this country, there have been several reports of successful treatment of the associated conditions. Notable among these is Holmes Sellors' report (1956) of 3 cases, the aneurysms being "congenital" in 2, and mycotic in 1. In Cleland's series of 40 cases of coarctation of the aorta treated surgically, berry aneurysms of the intercostal arteries were found in 6 patients and were sometimes multiple. There were 3 post-stenotic aortic aneurysms, one of them dissecting. One of the two patients with non-dissecting aneurysm also had infective endo-aortitis. An interesting feature of the series was that 8 patients had vegetations at the site of the coarctation, one of them frank bacterial endo-aortitis, and one had a positive culture of *Streptococcus viridans* from the vegetations.

5 of the 8 patients had fever pre-operatively, but no other evidence of infection (Cleland *et al.*, 1956).

The aneurysm in the present case was undoubtedly mycotic. Apart from its treatment, it was similar to a case of Maude Abbott's in which death resulted from rupture into the left main bronchus (Abbott, 1936). Incidentally, Abbott considered that all 14 associated aneurysms in her series of 200 coarctations were mycotic. Clearly our patient was at risk after his massive hæmoptysis while awaiting operation, and greatly at risk during operation till the aorta was controlled above and below the lesion. Having dealt with the aorta, removal of the aneurysm was done because of its size and bronchial communication. Parts of its wall were already inflamed. In the classical case report of Lam and Aram (1951) the patient died six weeks after operation from suppuration in the sac of an aneurysm which had not been excised. Considerable attention has been given to the length of time the aorta can be clamped without endangering the peripheral circulation, notably the renal and spinal blood flow. Rob (1955) considers that the lower thoracic aorta may be clamped safely for one hour at a body temperature of 28° C., and that two hours is getting near the danger point. Because of the collateral circulation few cases of paraplegia resulting from resection of the aorta for coarctation have been reported, but there are cases where this disaster has happened (Gross, 1953). For this reason we record that in our patient in whom six pairs of intercostal arteries had to be sacrificed, the descending thoracic aorta was clamped continuously for two hours at a body temperature of 30° C. with impunity.

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Multiple Islet Cell Carcinomas of the Pancreas.—Rodney Smith, M.S., F.R.C.S.

D. H., aged 53, labourer. Admitted December 17, 1955.

History.—In 1952 a tumour was removed from the left lateral wall of the pelvis, said to have been a *leiomyoma*. A few months ago a swelling in the right parotid gland appeared. A superficial fragment was removed under local anæsthesia by a casualty officer. Histology showed normal parotid tissue.

Present complaint.—"Blackouts" recurrently for four months. On questioning, story characteristic of spontaneous hypoglycæmia occurring with fasting and exercise.

On examination.—(1) Epigastric mass, size of fist, moving with respiration. (2) Smooth, circumscribed tumour in the right parotid gland.

Investigation.—Blood sugar on admission 46 mg.%. Exercise after fasting overnight produced early hypoglycæmic symptoms. Blood sugar at this stage: 17 mg.%. Attack promptly aborted by giving sugar.

Laparotomy.—(*a*) Multiple discrete, encapsulated tumours scattered throughout the pancreas, each apparently typical of an islet cell tumour. (*b*) Multiple discrete encapsulated tumours scattered throughout the liver. One very large tumour occupying most of the left lobe.

Procedure.—Subtotal distal pancreatectomy, leaving only a small part of the head of the gland. This was mobilized with the duodenum and when palpated an additional tumour within it could be felt. The pancreas was incised and this tumour enucleated. The large mass in the liver was excised by enucleation. The abdomen was closed with drainage.

Post-operative course.—Uneventful convalescence. All symptoms disappeared and glucose tolerance curve became mildly diabetic in character.

Second operation.—Tumour removed from right parotid gland.

Histological reports.—Subtotal pancreatectomy specimen contained seven islet cell carcinomas. The tumour enucleated from the head of the pancreas showed the same histology, as did the mass from the liver. The tumour from the parotid gland was also a secondary islet cell carcinoma. The slide of the tumour removed in 1952 was secured for examination. This also proved to be a secondary islet cell carcinoma, though removed three years before hypoglycæmic symptoms began.

Progress.—The patient remained well for only a few months but then relapsed with renewed hypoglycæmic attacks, and died in July 1956.

(A full account of this case is to be published in the *British Journal of Surgery*.)

Ligation of the Cœliac Axis and Superior Mesenteric Artery During Resection of an Upper Abdominal Aneurysm.—KENNETH OWEN, F.R.C.S. (for Professor C. G. ROB, M.C., F.R.C.S.)

H. T., aged 35, was admitted to hospital in June 1955 complaining of upper abdominal pain radiating to the back, and was found to have an upper abdominal aneurysm. He had a history of a probable spirochætal infection in 1944 and his W.R. and Kahn were positive. He was treated with 8,000,000 units of penicillin.

Three months later the aneurysm was exposed at laparotomy by Mr. Harold Edwards. It was found to be arising from the upper abdominal aorta and was wired (Fig. 1). It

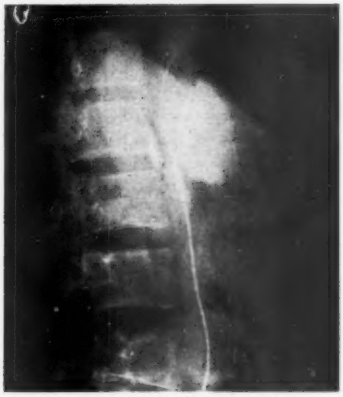

FIG. 1.—Pre-operative aortogram showing upper abdominal aortic aneurysm.

enlarged further, however, and the patient was referred by Mr. Harold Edwards to St. Mary's Hospital where a second operation was performed in January 1956 (C. G. R. and K. O.) through a left thoraco-abdominal incision. The operation was performed under hypothermic anæsthesia (Dr. C. A. Cheatle), the patient's temperature being reduced to 28° C. by means of external cooling. The aneurysm was exposed and the three branches of the cœliac axis and the superior mesenteric artery were found to be thrombosed. They were divided and ligated. The aneurysm was resected and replaced with a polyvinyl sponge implant from the diaphragm to the level of the renal arteries.

Despite the ligature of these arteries, there seemed to be an adequate circulation to the upper abdominal viscera. He made a straightforward post-operative recovery and liver function tests performed two weeks after operation were within normal limits. A post-operative aortogram (Figs. 2 and 3) showed an enlarged inferior mesenteric artery which

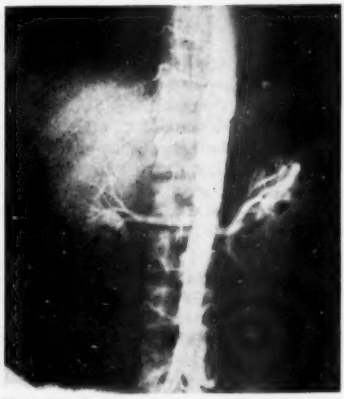

FIG. 2.—Post-operative aortogram showing polyvinyl implant, hypertrophied intercostals and inferior mesenteric artery.

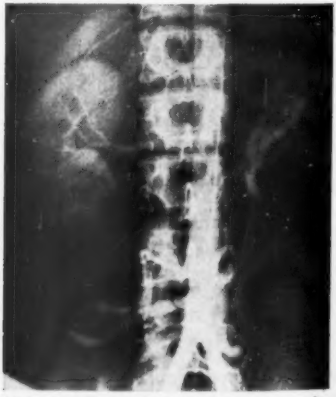

FIG. 3.—Post-operative aortogram showing the collateral circulation from the inferior mesenteric artery.

appeared to be the main supply to all the abdominal viscera apart from the kidneys. The main root of the collateral circulation to the upper abdominal organs would appear to be through the ascending branch of the left colic artery by way of the middle colic to the superior mesenteric artery. The lower intercostals were also seen to be enlarged on each side and it is probable that they are providing collaterals to the liver and upper abdominal organs. The collateral blood supply to the liver has been well described by Michels (1955), and the following vessels may well be giving a subsidiary supply to the liver in this case:

(i) The inferior phrenic artery.

(ii) The superior phrenic artery.

(iii) Terminal branches of the internal mammary artery through the falciform ligament.

(iv) Branches of the lower intercostal arteries entering the liver through the bare area.

The first similar case to be described was reported by Chiene in 1869. In his case the cœliac axis, superior mesenteric artery and inferior mesenteric artery were found to be thrombosed in a woman of 65 who had an abdominal aneurysm but who had died of another cause. She had developed an adequate circulation from the parietal branches of the aorta to supply her viscera. It is interesting to note that Chiene used this case as a vindication for cupping in the treatment of abdominal visceral disease, maintaining that the good anastomosis between visceral and parietal arteries allowed the congestion in the intestines to be relieved by cupping the abdominal wall.

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(1) **Parathyroid Tumour.** (2) **Recurrent Crohn's Disease.**—Mr. FRANK FORTY.

Extensive Small-gut Resection.—Mr. H. E. LOCKHART-MUMMERY.

Pyoderma Gangrenosum Complicating Chronic Ulcerative Colitis 11½ Years After Ileostomy.—Mr. NOBLE HUDSON.

Chronic Abscess of the Jejunal Mesentery Involving the Transverse Colon.—Mr. P. T. SAVAGE.

Unusual Type of Chronic Appendicitis.—Mr. C. KIRKHAM (for Mr. G. QVIST).

[*June* 8–9, 1956]

MEETING HELD AT THE ROYAL INFIRMARY AND AT THE WESTERN GENERAL HOSPITAL, EDINBURGH

The following Short Papers were read:

Carcinoma of Thyroid.—Mr. K. PATERSON BROWN.

Tumours of the Ampulla of Vater.—Mr. T. McW. MILLAR.

Polya-to-Billroth I Conversion.—Mr. HECTOR PORTER.

Some Radiosensitive Tumours.—Professor R. McWHIRTER.

Gravitational Ulcers.—Mr. C. W. A. FALCONER.

Metabolic Aspects of Endocrine Therapy and Adrenalectomy in Breast Cancer.—Dr. J. A. STRONG.

Unusual Lesions of the Intestines.—Symposium by Members of the Gastro-intestinal Unit, Western General Hospital.

Partial Gastrectomy in Relation to Acid Secretion and Parietal Cell Mass.—Dr. W. I. CARD.

The Cardio-œsophageal Junction.—Mr. H. BRUCE TORRANCE.

Noradrenaline in Shock.—Dr. J. TAIT.

Secretion Studies on a Gastric Cyst.—Mr. A. A. GUNN.

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Section of Anæsthetics

President—T. CECIL GRAY, M.D., F.F.A.R.C.S., D.A.

[*April* 6, 1956]

Buthalitone Sodium, Nitrous Oxide and Oxygen in a Series of One Hundred Dental Cases

By D. S. YOUNG, M.B., Ch.B., D.A., F.F.A.R.C.S.

IN dental anæsthesia none of the adjuvants to nitrous oxide which are commonly used such as premedication, ethyl chloride, Vinesthene and trilene has proved wholly satisfactory in my hands. Cyclopropane and oxygen will produce a peaceful, well-oxygenated patient but the high incidence of post-operative vomiting would seem a disadvantage.

Thiopentone followed by nitrous oxide and oxygen can give good conditions but the time taken by many patients to walk unaided even when minimal doses in the region of 0·1 to 0·4 gram are used, makes thiopentone impracticable in a busy surgery.

The work of Weese and Koss (1954, *Dtsch. med. Wschr.*, **79**, 601) on sodium 5-allyl-5-*iso*butyl-2-thiobarbiturate (called Baytenal in Germany) suggested that this agent might have a place in dental anæsthesia. This product is now available in this country under the name Transithal, and Buthalitone Sodium has been proposed as a common name.

It was decided to employ Buthalitone to abolish consciousness and to determine whether its residual effect made the subsequent maintenance on nitrous oxide and oxygen possible to conduct smoothly while using a greater percentage of oxygen than if no barbiturate had been given and at the same time obtain a rapid recovery.

The patients selected were those in whom it was felt that nitrous oxide and oxygen alone would not give quiet conditions on account of their type or teeth. Fit patients only were accepted and no premedication was used. The series was a strictly consecutive sequence including all cases in which Buthalitone was employed. There were 58 females and 42 males. Average age 39 years 9 months; the youngest patient was 15 and the eldest 57. 68 appeared to be calm and 32 were considered nervous. The average number of teeth removed per patient was just over fifteen and in 97 patients the proposed extractions were completed.

Buthalitone dosages: Average 0·46 gram; Maximum used 0·9 gram; Minimum used 0·3 gram.

The Buthalitone was made up as a 10% solution as recommended by the makers. The injection was made at a rate of 1 millilitre in 4 to 5 seconds until the estimated dose was given and a pause was made until consciousness was lost. Resistant cases in whom this initial dose had been insufficient sometimes required a further increment of up to half this amount prior to starting the nitrous oxide administration.

Before embarking on this series, attempts were made on preliminary cases to extract at this juncture but all reacted immediately or after only a few teeth had been removed. It is not considered that Buthalitone is likely to prove a satisfactory sole agent in dentistry because of the difficulty of the anæsthetist in having to control the airway and mouth gags and at the same time give further supplementary intravenous injections. Furthermore the larger total dose required would unduly prolong the recovery.

In the series described the induction was completed on 100% nitrous oxide; even so it was quite frequently seen that consciousness tended to return before the gas took effect. 5 cases came so light that they mumbled words but none remembered this afterwards.

Mouth breathing occurred in 13 cases and was countered by mouth occlusion.

The signs of the establishment of surgical anæsthesia were similar to those in which nitrous oxide and oxygen is used alone except that the extractions could be commenced without reaction at an apparently lighter level.

Two signs upon which most reliance was placed were the resistance of the eyelid to finger retraction which was nearly abolished and the eyeball movement which was watched until it almost stopped. At this point 5–10% oxygen was added, the mouth opened with a gag and a pack inserted. If no reaction occurred to the forceps the oxygen percentage was progressively increased and it was usual to maintain on 15–20% oxygen until the extractions were finished.

When the patients tended to come too light they were controlled without difficulty by reducing the oxygen by say 5%.

The completion of the induction of nitrous oxide averaged 1 minute 25 seconds with a maximum of 3½ minutes in a case which developed laryngeal spasm.

Apnœa was treated by manual ventilation, squeezing a reservoir bag with one hand and closing the nasal expiratory valve and mouth with the other while continuing the induction on nitrous oxide. The longest duration of apnœa was one minute.

The laryngeal spasms were mild and transient and while they persisted 20% oxygen was given. No spasm occurred in the 52 cases in which less than 0·5 gram Buthalitone was used.

The operating time averaged three minutes with a maximum of five.

The maintenance was remarkably easy and free from exertion on the part of anæsthetist and patient. 86 remained motionless throughout. 9 reacted by slight movement of the arms and were controlled easily by the nurse. 2 anæsthetics were interrupted and reinduced as the patients were becoming fractious. 1 was abandoned half-way because there was blood in the pharynx. 1 came light and vomited before she could be reinduced. 1 got out of control and was not completed. [The last 2 mentioned were numbers 99 and 100 in the series.]

The amount of hæmorrhage from the sockets as compared to that occurring with plain nitrous oxide and oxygen was assessed by the dentists from gross appearances.

70 showed diminished bleeding, 24 were similar in amount and 6 bled fairly markedly. No patients showed facial pallor or reduction in pulse volume suggesting a marked hypotension resulting from the barbiturate.

Blood pressure recordings were made in another series of 50 cases, before and after the Buthalitone injection. The biggest change in systolic pressure was 40 mm.Hg, and in no instance did it fall below 100 mm.Hg.

The return of consciousness after the operation was rapid. The period from ending the nitrous oxide administration to first speaking averaged 1 minute and 10 seconds with a maximum of 5 minutes where 0·8 gram of Buthalltone was used.

Immediately they spoke they were asked two questions. (*a*) "How do you feel?" (*b*) "How did you find that experience?"

Leading questions were avoided so as to get a true idea of their opinion of the technique. 99 of the answers were satisfactory, only one patient did not reply, a tearful woman who was obviously a poor type. The responses most frequently made were: (*a*) "I feel: all right; well; fine; champion. I was dreaming. I didn't feel a thing. I wondered where I was. I've been all over the place." (*b*) "That was easy; lovely; O.K.; fine; champion."

Some were amusing: "Give me some more and put them back." "I don't feel too bad but it's a bit early to say." "I enjoyed that pull out." "Wonderful dream; treble chance coming up next Wednesday."

The patients were coherent and rational almost as soon as they started speaking. Many were obviously euphoric and voluble in their appreciation of the injection in the arm as they call it. In a practice where this method is introduced it is soon noticed that this sequence raises morale and is requested in preference to "gas".

The time from commencing to speak to walking to the recovery room averaged 3 minutes 25 seconds with a maximum of 9½ minutes and a minimum of 1 minute. It could certainly have been reduced if the patients had been hurried out of the chair. 56 walked out steadily and unaided, 27 were lightly assisted and 17 were staggering.

The time from induction of anæsthesia to walking to the recovery room averaged 9 minutes, so if 2 minutes are allowed to prepare the patient and 2 minutes to give the Buthalitone and complete the induction, the time occupied on each case was only 13 minutes.

A further 10 to 15 minutes were spent in the rest-room to ensure that patients were absolutely steady and in full possession of their faculties before returning home and it was insisted that they were accompanied by a friend.

This sequence should only be undertaken by anæsthetists with experience of intravenous techniques and their complications who are also familiar with the administration of dental anæsthetics in the surgery. This method should not be used by the dentist or general medical practitioner without previous special training.

[A film was shown of the technique in 4 cases.]

Dr. J. M. B. Pooley stated that the makers had provided him with a sample of sodium 5-allyl-5-*iso*butyl-2-thiobarbiturate. He had tried it in manipulative and other short procedures, but had found anæsthesia uncertain to non-existent, and had been asked to desist from trials by his surgeons. This was using it as a single dose "one shot" technique.

He believed that there might be a place for the drug as an induction agent for children about to undergo tonsillectomy. This was because respiratory depression was of so short duration that it was easy to continue with G.O.E. This in his experience reduced bleeding, and overcame objections to a combined barbiturate and relaxant anæsthetic.

Dr. H. C. Churchill-Davidson said that in his film Dr. Young had omitted to insert a "prop" between the teeth before the induction of anæsthesia. In his own experience, using an ultra-short-acting barbiturate in similar doses, occasionally the jaw muscles did not relax and the teeth remained tightly clenched unless the supplementary nitrous oxide anæsthesia was pressed to a dangerous level of anoxia. He was not convinced, therefore, that the use of a barbiturate for induction of anæsthesia dispensed with the necessity for inserting a "dental prop" while the patient was conscious.

Dr. J. G. Bourne said that Buthalitone had been called a "lightning" drug. His observations were very incomplete but seemed to show that it was a little less than half as strong as thiopentone, and in equipotent dose lasted rather longer.

Dr. T. A. B. Harris, Director, Department of Anæsthetics, Guy's Hospital, London, gave a talk on **Barbiturate Antagonists.**

Section of Radiology

President—E. Rohan Williams, M.D., F.R.C.P., F.F.R., D.M.R.E.

[*March* 16, 1956]

Radiology of the Newborn Infant[1]

PRESIDENT'S ADDRESS

By E. Rohan Williams, M.D., F.R.C.P., F.F.R., D.M.R.E.

Whilst Pædiatric Radiology has shared in the great advances in radiology generally in the last twenty-five years, it is only in quite recent years that much work has been done with newborn infants. The thought of pædiatricians has changed markedly away from the "no touch" attitude and radiological help is being increasingly sought in neonatal problems in children's hospitals, in large maternity hospitals and in general hospitals with maternity units. Any one of us may have to meet a diagnostic problem in a young infant—a baby's life may depend on gentle and efficient radiography and on skilful interpretation. There is seldom an opportunity for a deliberate and thoughtful re-examination—usually the first films taken must be decisive.

Our help will be called upon mainly in respiratory problems, acute abdominal crises, birth injuries and skeletal deformities and dysplasias.

In this paper, I shall have to confine myself to the respiratory and abdominal conditions.

The Chest in the Newborn Infant

The normal chest.—There are a number of features which may give rise to difficulty in the judgment of the normality of the neonatal chest. Firstly, the extreme difference in the visual appearances between deep inspiration and full expiration: on expiration, there is considerable de-aeration throughout the lungs and thus diffuse opacification of the lung fields: it is difficult to define the diaphragmatic cupolæ. It will readily be appreciated that, with the lack of contrast from the pulmonary air and poor visualisation of the diaphragm, it is difficult to differentiate between mere expiration and either diffuse anectasis (Marriott's term for non-expansion of the lung) or secondary atelectasis. Secondly, the heart is relatively larger than in the adult and may encroach appreciably on to the lung fields. Thirdly, the normal superior mediastinal width is very variable, depending on the degree of expiration or inspiration, the size and site of the thymus and on whether there has been a bout of crying or apnœa. Further, I am sure that in many infants there is a laxity of the mediastinum so that it may wander from side to side in slight measure. Owing to the relatively great breadth of the thorax and its lesser relative height (in comparison with the adult), the vascular markings spreading from the hila appear to be straighter running and are disposed radially through a less wide sector than in the adult.

Extraneous skin lines can be most puzzling and may at times lead one, even after the most careful scrutiny, to the erroneous conclusion that a pneumothorax is present.

Radiography of the Newborn Chest

The attainment of radiographs of the highest quality is of the greatest importance in chests of newborn infants. All of us have to accept and report on chest films of adults which are below the quality we would wish. But such acceptance is not to be condoned in neonatal chest radiographs. I do not think one can justifiably offer a firm or even a tentative opinion on the chest film of a newborn infant that is taken with any rotation of the thorax and in any respiratory phase other than moderately or fully deep inspiration.

The production of adequate radiographs—that is excellent radiographs—calls for patience, skill, gentleness and a genuine interest on the part of the radiographer.

There are enough puzzling features about the newborn infant's mediastinum, heart and lungs with which to wrestle without facing technical shortcomings. In normal infants, there is so much variation in the mediastinal breadth, the cardiac size and shape and the thymic size that we must be able to rely on accurately positioned and centred films to make any worth-while judgment. At Queen Charlotte's, it is our custom to take a minimum of two A.P. films and a lateral film of the thorax. None of the films taken is discarded by the radiographer, and all come for my inspection.

Respiratory Anxiety and Distress

Radiological help is sought more often when respiratory anxiety is felt than in any other field in neonatal work. The problems of *respiratory distress* are complex but in recent

[1]This paper is abridged. 60 illustrations were shown.

years, much light has been thrown on physiological disorders of respiration, and radiology has certainly played its share in these advances.

What do we mean by respiratory anxiety and distress? Respiration may be difficult to establish immediately after birth: when established, breathing may be erratic, arrhythmic and grunting: there may be very rapid, regular and shallow respirations: there may be cyanosis. On inspection of the thorax, there may be inspiratory retraction of the intercostal spaces and retraction of the whole sternum. In the very young infant, respiration is mainly diaphragmatic and abdominal.

In the normal infant at birth, respiratory rate and the volume of tidal air are very variable: irregular respiration is common, including periodicity of a Cheyne-Stokes type, especially in normal premature babies. If the respiratory rate increases, periodicity and arrhythmia often disappear, as Cross has pointed out. Thus newborn infants with gross pulmonary lesions usually show rapid and regular respirations. Clement Smith (1955) has emphasized that retraction of the chest wall, especially in premature babies, is not necessarily evidence of insufficient pulmonary aeration. The distended thorax, with bulging of the intercostal spaces and forward prominence of the sternum may be found with a "trapped-air" syndrome and be much more disadvantageous than the pulmonary condition with retraction of the chest wall.

Thus the clinical assessment may be far from easy and radiological examination may throw considerable light on the underlying pulmonary lesions.

The Radiological Findings in Respiratory Distress

We owe a debt to a small number of workers who have materially advanced our knowledge concerning the radiology of the newborn chest in recent years—notably to Donald and Steiner (1954), to Mayer in France and to Peterson and Pendleton (1955).

A chest radiograph in a respiratorily-distressed infant may show one of the following patterns:

(1) *Normal Appearances*

(2) *Homogeneous Opacity*. This may be localized or widespread.

(*a*) *Localized.*—(i) Anectasis or primary atelectasis of a segment or lobe. (ii) Varying and migrating atelectasis or consolidation of a segment or lobe—not present at birth.

(*b*) *Generalized.*—(i) Widespread anectasis or primary atelectasis. (ii) Widespread secondary atelectasis with hyaline membranes. (iii) Confluent pneumonic consolidation.

(3) *Non-homogeneous Opacities*

(*a*) Widespread coarse mottled opacities of irregular distribution with some translucencies, associated with aspiration of liquor and meconium, perhaps with a reactionary pneumonia.

(*b*) Widespread fine reticulo-granular shadowing associated with hyaline membranes.

(4) *Expanded or Contracted Thoracic Parietes*

I cannot stress too strongly that a recognizable pattern may change very rapidly: indeed, Steiner (1954) has suggested that a sequential change in specific patterns is the best evidence to justify a diagnosis of hyaline membranes radiologically. In those infants that die, much may have happened in the lungs in the interval of perhaps no more than one or two hours between the last radiographic examination and death. Thus, even with an immediate post-mortem "follow-up", it may be very difficult to decide which of the numerous pathological processes found was mainly or dominantly responsible for the abnormal changes seen in the radiographs.

By indicating the "patterns" that may be found, I do not wish in any way to over-simplify the solution of the problems but to indicate to radiologists the broad visual appearances that may be encountered. The multiplicity of the pulmonary lesions will often make the dogmatic diagnosis of individual types of lesions the province of the clairvoyant radiologist except in certain rather specific instances. Landing (1955) gives us an appreciation of the

Legends

Fig. 1.—Anectasis (primary atelectasis) of the left upper lobe.

Fig. 2.—To show a difficult differential diagnosis between anectasis of the right upper lobe and either pathological or non-pathological widening of the mediastinum. Three days later there were wholly normal appearances.

Fig. 3.—To show difficult differentiation between anectasis of the left upper lobe and mediastinal widening. The accent is in favour of the former—note that no aeration is seen in the anterior lung margins.

Fig. 4.—Premature breech delivery; birth weight 3½ lb. Slight to moderate respiratory distress. A.—Film at fourteen hours—very poor aeration throughout both lungs. B.—Film at thirty-two hours, considerable improvement. C.—Film at sixty-two hours, continuing improvement. Thereafter uninterrupted recovery. An example of extensive anectasis associated with prematurity.

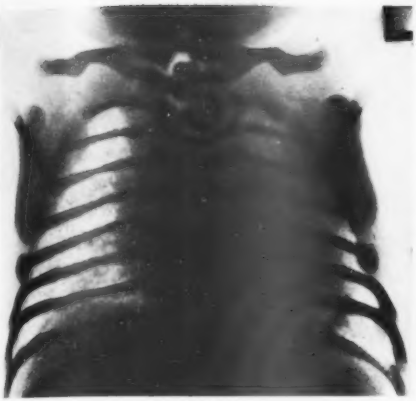

FIG. 1.

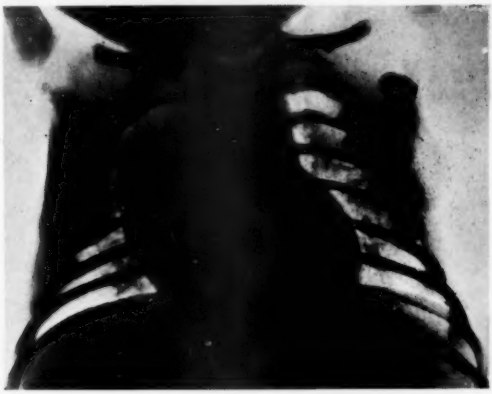

FIG. 2.

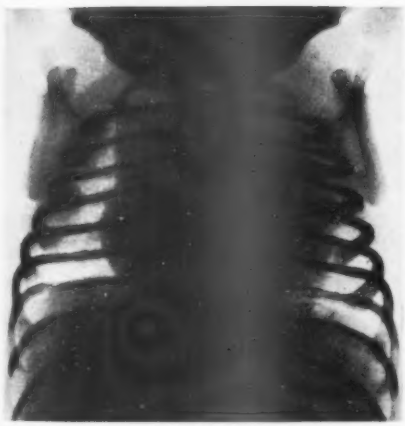

FIG. 3A.

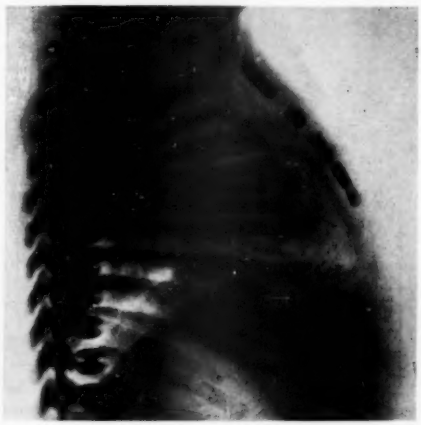

FIG. 3B.

FIG. 4A.

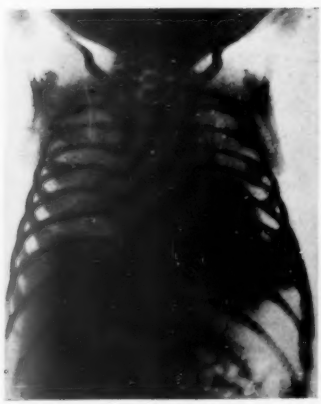

FIG. 4B.

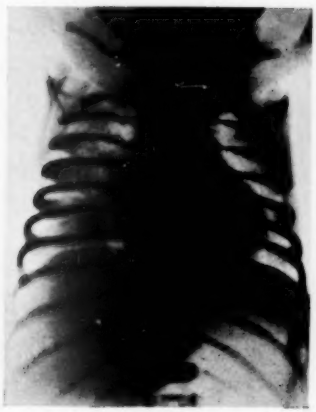

FIG. 4C.

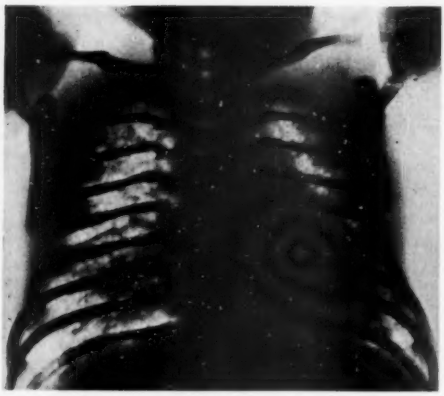

FIG. 5.

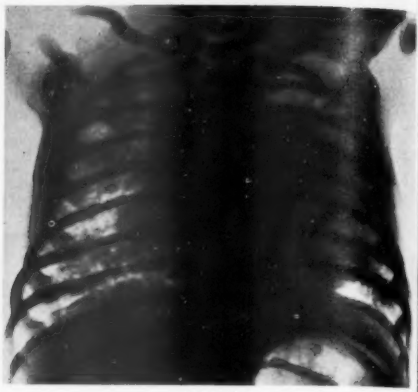

FIG. 6.

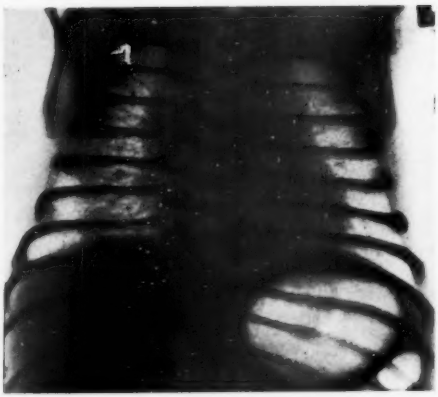

FIG. 7.

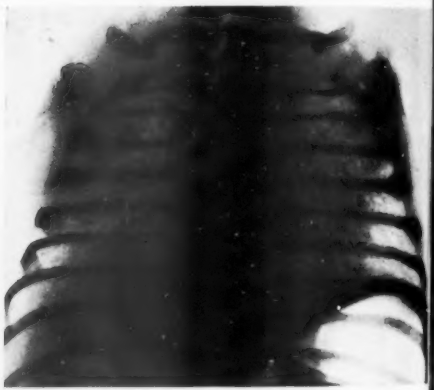

FIG. 8.

FIG. 9A.

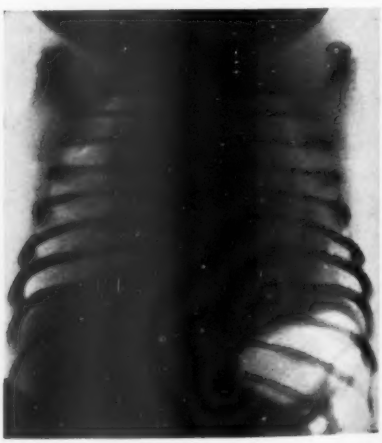

FIG. 9B.

problem. Of 178 successive post-mortem examinations on infants who died before the seventh day, in 152 cases (85%) major pulmonary lesions were found (Table I).

The same observer, Landing, has reported that in detailed post-mortem examinations of the lungs in 125 successive neonatal deaths, the following lesions were present (Table II):

TABLE I

Aspirated amniotic sac contents (including hyaline membranes)	81	45%
Pneumonia	39	22%
Hæmorrhage	23	13%
Gross prematurity	4	2%
Œdema	3	2%
Atelectasis	1	0·5%
Malformations	1	0·5%
	152	

TABLE II

Lesion	Percentage present	Percentage severe
Atelectasis	77	15
Emphysema	73	2
Hæmorrhage	68	19
Interstitial emphysema	67	7
Amniotic material ..	63	15
Immaturity	53	24
Œdema	46	3
Hyaline membrane ..	37	19
Pneumonia	33	13
	517	117

It is very evident that, whilst there will probably be one dominant lesion, multiple lesions are the rule: indeed, in the average neonatal death, an individual infant is likely to show four subsidiary lesions. Thus detailed radiological analysis is beset with profound difficulties. Of the listed lesions, nine in number, the following would cause pulmonary opacities: atelectasis, hæmorrhage, amniotic aspiration, œdema, hyaline membranes and pneumonic consolidation. Alveolar and interstitial emphysema would cause abnormal translucencies.

I need not labour the problems of precise diagnosis in many cases, but in an appreciable number due consideration of the antenatal and natal history (with especial reference to prematurity, postmaturity and fœtal distress), the respiratory behaviour from the moment of birth and the radiological appearances will help the radiologist towards the truth in the problems of respiratory distress.

To return to the radiological findings in respiratory distress.

(1) *Normal Appearances*

An infant giving cause for respiratory anxiety and in whom there are normal pulmonary appearances may well have a cerebral cause for the distress. Intraventricular hæmorrhage may well be present. Forceful pulmonary ventilation in such a case, as Donald has stressed, would not only be valueless but probably harmful.

(2a) *Localized Homogeneous Opacity*

(i) *Segmental or lobar anectasis, i.e. primary atelectasis or failure to expand.*—This condition may be easy to recognize, especially in the lower lobes, but I believe that isolated lower lobe anectasis is uncommon in the newborn. When affecting one of the upper lobes, the recognition may be very difficult, mainly because of the great variation in the superior mediastinal width even in films of impeccable quality. The more complete the airlessness

Legends

FIG. 5.—Full term delivery; weight 9 lb. 4 oz. Meconium staining of liquor one and a half hours before delivery. Infant cyanosed with rapid shallow respirations. Film at seventeen hours: widespread coarse mottling probably due to aspiration of liquor and meconium. Slow clinical and radiological improvement—lungs not clear until sixteenth day.

FIG. 6.—Full-term spontaneous delivery: breathing not rapid but marked retraction and some cyanosis. X-ray—second day: shows widespread coarse mottled opacities. Death on same day—*P.M. examination*—widespread inhaled liquor with squames and meconium bodies. Pneumonic reaction to inhaled contents.

FIG. 7.—Spontaneous premature labour at the thirtieth week. There was considerable respiratory distress. X-ray at one and a half hours showing a striking reticulo-granular pattern. Death occurred at the thirtieth hour. A P.M. examination was refused but a pulmonary biopsy specimen was secured. The typical appearances of hyaline membrane were reported by Dr. Claireaux.

FIG. 8.—Spontaneous delivery at the thirtieth week. There was meconium stained liquor three hours before delivery. The infant was cyanosed with irregular grunting respirations. Improved with oxygen, then deteriorated. X-ray at eight hours: a reticulo-granular pattern almost masked by widespread secondary atelectasis. Death at twelfth hour. At P.M. examination there was extensive hyaline membrane with secondary atelectasis and also evidence of aspiration of liquor. Note the visualization of air in second and third order bronchi.

FIG. 9.—Spontaneous delivery at 32 weeks. Weight 4 lb. 10 oz. Cried immediately at birth—no initial respiratory embarrassment but this was evident later on first day. There were severe cyanotic attacks. Film first day (left) shows reticulo-granular pattern. Film second day (right): the degree of secondary atelectasis was greater. Thereafter rapid recovery with chest almost clear radiologically on third day.

in the upper lobe, the more difficult is the decision (Figs. 1, 2 and 3). I suspect that I have often reported primary atelectasis of an upper lobe when none has been present. Such babies, if significantly distressed at all, will usually be distressed from birth. Expansion will usually be rapid with appropriate ventilation measures.

(ii) *Varying and migrating consolidation or atelectasis of a segment or lobe.*—Here there is often no distress in the first few hours or days after birth: sometimes more than one segment is affected and, on serial observations, there is a tendency for resolution to occur at one site while a fresh lesion is developing elsewhere—a migratory tendency. I believe that segmental atelectasis can also behave in this manner but I doubt if, on radiological grounds, the pneumonias and the atelectases can be differentiated when small volumes of lung are affected.

(2*b*) *Generalized Homogeneous Opacities*

(i) *Widespread anectasis or primary atelectasis.*—There is severe respiratory distress from birth: the thorax shows no bulging and recession may be extreme. Radiologically, there are almost total ground-glass opacities in the lung fields. Slight peripheral basal aeration may be sometimes seen (Fig. 4). It is amazing that babies with such appearances can live, even if only for a few hours, but the considerable swallowed air in the stomach and intestines must provide the route for oxygenation.

(ii) *Widespread secondary atelectasis with hyaline membranes.*—In infants dying with hyaline membranes, in the later stages the lungs will become almost uniformly opaque but the thorax is generally expanded with a forward prominence of the sternum.

(iii) *Confluent pneumonic consolidation.*—When an infective pneumonia has become widespread and confluent, the infant will usually be *in extremis* and radiological examination is unlikely to be requested.

(3*a*) *Non-homogeneous Opacities—with Widespread Coarse and Irregular Shadowing*

(i) *Infective bronchopneumonia* is usually encountered in the later neonatal period and is mainly seen in the dorsally situated segments of the lungs, especially in the lower lobes.

(ii) *Aspiration of amniotic material, with or without meconium.*—There is a widespread coarse mottling of irregular distribution with small patchy transradiant areas (Figs. 5 and 6). The thorax is expanded, sometimes with forward prominence of the sternum.

Clinically and radiologically there is usually rapid improvement but the radiological clearance tends to lag behind the clinical betterment. The baby is usually fully mature or post-mature and there is frequently a history of fœtal distress during the labour.

This is the *fœtal aspiration syndrome*. In the few cases that come to post-mortem examination, there is gross aspiration of keratinized squamous cells from the liquor and meconium is sometimes present in the bronchioles and alveoli. Focal alveolar atelectasis and emphysema are found. Occasionally, there is a non-infective reactive pneumonia.

(3*b*) *Reticulo-granular or Fine Miliary Pattern*

There is a general increase in density throughout the lung fields with a fine granular and reticular striational pattern. Usually both lungs present similar overall densities, but the changes may be more emphatic on one side than on the other. The chest is well expanded, often with forward sternal bulging as seen in a lateral radiograph. The bronchial tree is often well filled with air which can be traced into bronchi of the third and fourth order, almost out to the periphery, a feature seldom seen in widespread anectasis or primary atelectasis (Figs. 7, 8 and 9).

If the infant whose lungs show these changes has been radiographed in the first hour of life, the lungs are likely to present normal appearances. Once the reticulo-granular pattern has developed, it is likely to become accentuated in the first twenty-four to forty-eight hours: if the infant survives, the changes gradually clear and no lesions are apparent by the fifth to the seventh day.

If the respiratory distress worsens, this delicate but nevertheless rather striking pattern may rapidly become obliterated because of increasing secondary alveolar airlessness and ultimately the lungs become almost homogeneously opaque.

Amongst babies showing such appearances, there will be a high proportion of premature births and of deliveries by Cæsarean section. At post-mortem, hyaline membranes are

Legend

FIGS. 10 and 11.—Normal delivery at 36th week. A weakly infant not showing any respiratory difficulty until twelfth day when developed grunting and very rapid respirations. Film on twelfth day (Fig. 10) shows right-sided effusion and ? extensive pneumonia. Also a spherical opacity seen through the cardiac shadow. On needle exploration of the right pleural cavity, purulent fluid withdrawn—*Staphylococcus aureus* organisms. Twentieth day—no fluid remains in right pleura but there is a small pneumothorax. The left basal lesion now shows a multilocular air-containing cavity. Film on twenty-fifth day (Fig. 11) shows a large tension cavity at the left base. This subsequently decreased steadily in size. An example of a staphylococcal pneumonia and empyema—with an abscess in the left lower lobe which became a tension cavity.

FIG. 10A.

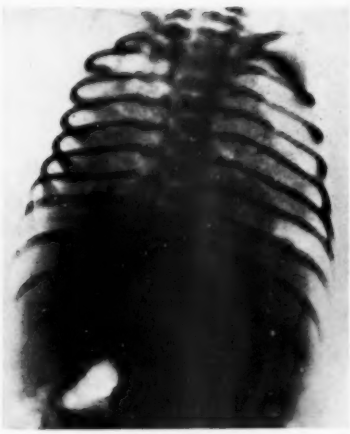

FIG. 10B.

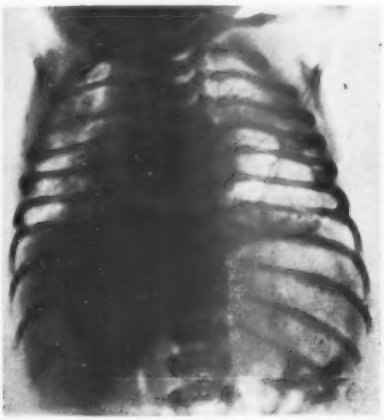

FIG. 11A.

FIG. 11B.

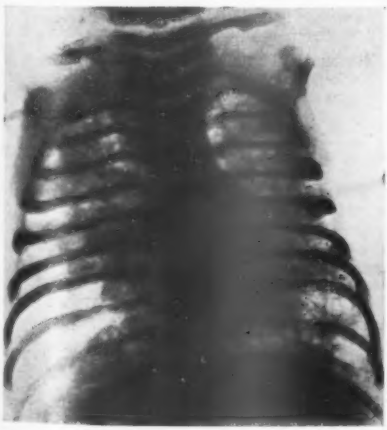

FIG. 12.—The mother was a primigravida with toxæmia. At the thirty-eighth week there was an artificial rupture of the membranes. The subsequent labour ended in Cæsarean section because of inertia. The baby was well until the fourth day when it developed a bad conjunctivitis, treated with Chloromycetin. On the eighth day the infant collapsed with severe cyanosis and marked pulmonary physical signs. Film on eighth day shows widespread irregular coarse mottling. Death on the ninth day. At P.M. there were massive bilateral pulmonary hæmorrhages as the sole explanation of the radiological appearances.

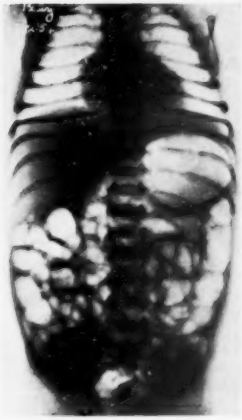

FIG. 13A.

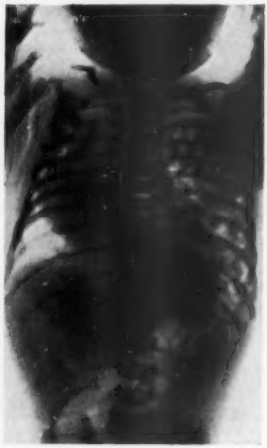

FIG. 14A.

FIG. 15A.

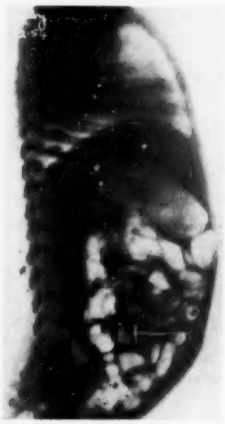

FIG. 13B.

FIG. 14B.

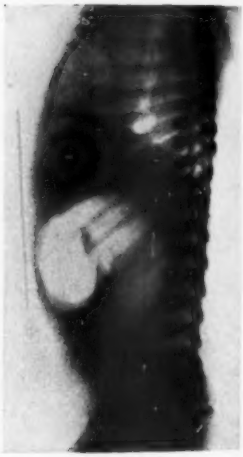

FIG. 15B.

FIG. 13.—Infant born prematurely at 31 weeks. Had several small bile-stained vomits with slight distension. Meconium passed on third day. Films on fourth day. No frank abnormality but general gaseous "fullness". Mother on Ansolysen for hypertension in pre-eclamptic toxæmia. This case illustrates the difficulties sometimes caused by Ansolysen treatment. Clinically suspicious of obstruction—radiologically not so.

FIG. 14.—Normal vertex delivery—weight 6 lb. 7 oz. Blue asphyxia—mild repeated cyanotic attacks. Cardiac impulse on right side, breath sounds only heard on right. Initially, normal respiratory rate and rhythm but later increasing respiratory distress. Film at thirty hours—diagnosis of partial absence of left diaphragm with abdominal viscera in left hemithorax. Transferred to Gt. Ormond Street Hospital. At operation, Professor R. S. Pilcher found sufficient diaphragm remnant to allow closure after returning the viscera to the abdomen. At 3 months, infant well, weight 11 lb. 14 oz. with no abnormal physical signs in chest and no intestinal shadows in chest.

FIG. 15.—Premature birth at 32 weeks. Vomited bile-stained mucus at twelve hours. Film at sixteen hours—diagnosis of duodenal atresia. Second X-ray at forty hours—no essential change. Transferred to Gt. Ormond Street. Duodeno-jejunostomy performed. Death the next day.

likely to be demonstrable lining dilated alveolar ducts, terminal bronchioles and some alveoli. There is widespread resorption atelectasis in the alveoli.

Peterson and Pendleton (1955) have written in a convincing manner of the justifiable recognition of two distinct syndromes which will be found only in the newborn infant.

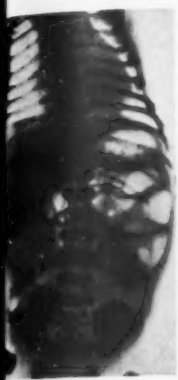

FIG. 16A.

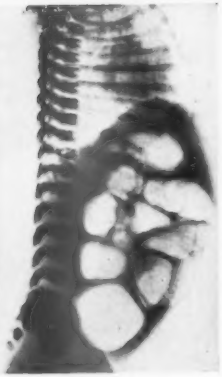

FIG. 16B.

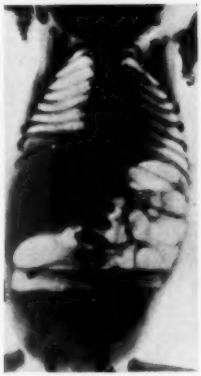

FIG. 17A.

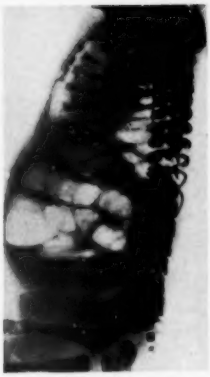

FIG. 17B.

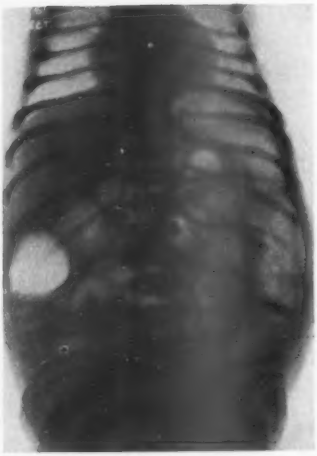

FIG. 18A.

FIG. 18B.

FIGS. 16 and 17 (Supine and erect).—Early definite abdominal distension. Vomiting of meconium on first and second days. Film on second day—diagnosis of complete small gut obstruction in middle or lower small gut. Transferred to St. Bartholomew's Hospital. Complete atresia half-way down small gut found. Side-to-side anastomosis of small gut to transverse colon performed. Subsequent increasing cyanotic attacks and death. P.M.—anastomosis patent, also whole colon patent. Atresia confirmed.

FIG. 18.—Delivery by lower segment Cæsarean section for fœtal distress. Weight 7 lb. 2 oz. Third day—slight vomiting. Fourth day—increasing vomiting, upper abdominal distension and visible peristalsis. Film on fourth day shows low level small gut obstruction. Fifth day—death. At P.M.—small gut volvulus with 270 degree rotation and distension of approximately 100 cm. of gut.

We thus have, firstly, the *hyaline membrane syndrome* with the accent on prematurity and delivery by Cæsarean section. The credit for recognizing that the specific radiological appearances were due to hyaline membranes belongs to Steiner, working with Donald and Claireaux.

Secondly, we have the *fœtal aspiration syndrome*, with the radiological characters recognized by Peterson and Pendleton, associated with postmaturity, fœtal distress and the passage of meconium into the liquor. The prognosis in the fœtal aspiration syndrome is appreciably better than in the hyaline membrane syndrome.

For a long time I seriously doubted whether one had the right to assume that the normal pulmonary pattern in a very premature infant was similar to that of a fully mature infant. This doubt remained until I had carefully reviewed a series of chest films of premature infants without respiratory distress and until I had surveyed all the material available at Queen Charlotte's Hospital specifically for this Address. I now believe, as Steiner concluded

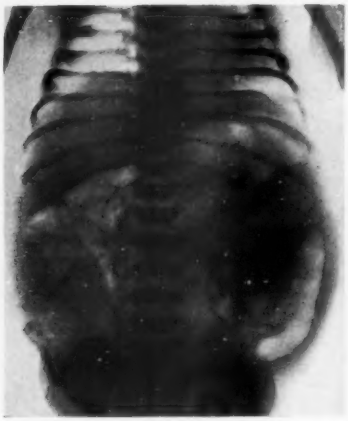

FIG. 19A.

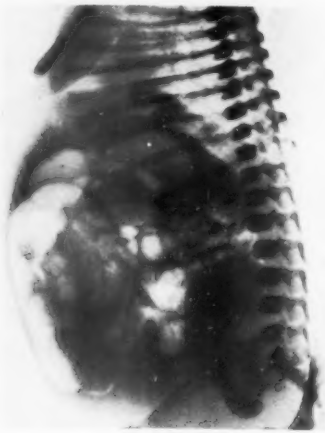

FIG. 19B.

FIG. 20A.

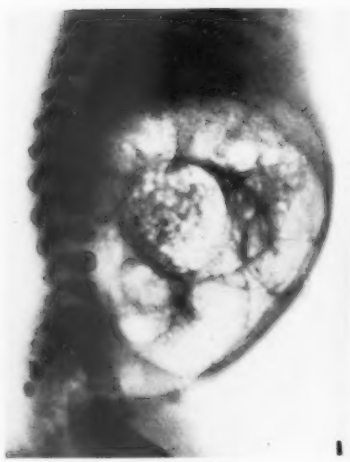

FIG. 20B.

FIG. 19.—Full-term normal delivery—weight 6 lb. 10 oz. Thirty-six hours—increasing abdominal distension, vomited and no meconium had been passed. X-ray shows a peculiar gut pattern with distension by gas and solid material—but no real admixture. Tentative diagnosis of meconium ileus. Transferred to Gt. Ormond Street and operation by Mr. G. H. Macnab. Both small and large gut distended by meconium which was squeezed out of an ileostomy opening—190 grams being extruded. Death on fourth day. P.M.—meconium ileus confirmed with fibrocystic disease of pancreas.

FIG. 20.—Full-term delivery—weight 7 lb. 3 oz. Sixteen hours—abdominal distension marked, no vomiting, had passed meconium. Twenty-three hours—increasing respiratory distress. X-ray—gross colonic distension with solid material and gas. Twenty-eight hours—death. Post-mortem examination—gross colonic distension down to rectum (inclusive). Small gut unaffected and no organic obstruction or volvulus found. Apparently an idiopathic dilatation of the colon without a narrowed aganglionic segment—perhaps not strictly acceptable as a Hirschsprung's disease in the modern concept.

two or three years ago, that the normal pattern of the lungs of a premature infant does not differ from that of a fully mature infant.

The origin and nature of hyaline membranes is a matter of much argument and controversy. Recently, new light has been thrown on the possible ætiology. Lynch and Mellor (1955) have shown that the staining reaction of hyaline membrane is the same as that of granules in the epithelial cells lining the respiratory bronchioles: that the stainable material

was much greater in these cells in lungs showing hyaline membranes than in control lungs without membranes: that amongst the controls, the stainable material was much more plentiful in lungs of premature than mature infants. They conclude that hyaline membrane is an excess of secretion from the epithelium of respiratory bronchioles and suggest that this secretion may be concerned with the transference of oxygen to the blood, that oxygen may provide the stimulus necessary to produce membrane and that the amount of secretion is proportionate to the oxygen concentration. Hyaline membrane is never found in infants who have died within one hour of birth.

Administration of oxygen in high concentration may well be a cause of hyaline membranes as well as of retrolental fibroplasia. In premature infants, the use of a low oxygen concentration with high humidity is urged in treatment. (At this stage in the Address the author showed illustrations of a number of interesting pulmonary conditions in the newborn only two of which can be included here (Figs. 10, 11 and 12).)

The Abdomen (Figs. 13–20)

I do not propose systematically to review the radiological findings in neonatal abdominal emergencies. There have been two excellent papers in this field in recent months—that by Hajdu (1955) and Macnab (1955).

Firstly, I wish to consider the clinical signs and symptoms of obstructive lesions together with the commoner atypical features—the important exceptions to customarily accepted rules. Secondly, I shall discuss the normal appearances of the alimentary tract in the first few hours after birth. Finally, I shall give illustrations and brief histories of some neonatal emergencies I have seen at Queen Charlotte's Hospital in recent years.

The symptoms and signs of neonatal obstructive lesions indicating an emergency state are:

(1) Vomiting and repeated regurgitation.

(2) No passage of meconium.

(3) Abdominal distension, which may be due to:
   (*a*) intraperitoneal fluid—as in hydrops fœtalis and meconium peritonitis,
   (*b*) gaseous distension in the stomach, duodenum, small or large intestine,
   (*c*) distension of the gut owing to solid or semi-solid contents,
   (*d*) non-alimentary conditions such as bladder distension in congenital atresia of the bladder neck, congenital cystic kidneys and various types of retro-peritoneal hæmorrhage.

(4) Excessive peristalsis of the gut or a lack of peristaltic activity.

It is universally agreed that the earlier the diagnosis, the more favourable the prognosis in the diseases which go to make up "the acute abdomen". If this is true in adults, it is emphatically so in the newborn infant, in whom the prognosis is much worsened once dehydration has begun. In intestinal obstructive states, even in collectively the best surgical hands, an infant has only a 1 in 4 chance of survival. The early use of radiological examination and wider knowledge concerning interpretation will surely help towards improving the prognosis in this field. In many types of obstruction in the newborn, the obstruction has been operative for an appreciable time before birth: what would appear to be an acute obstruction is indeed the post-natal manifestation of a chronic obstruction.

Following Macnab, let us consider some of these clinical features critically.

Vomiting.—Vomiting is common in obstruction but is often delayed, as long as two to three days in 20% of cases of intestinal atresia, and as long as two weeks in 50% of cases with incomplete intestinal stenosis. It is important to note the presence or absence of bile in the vomit. The combination of bile-stained vomiting and no passage of meconium is, in Macnab's view, diagnostic of organic obstruction. In 40% of the cases of intestinal atresia in Louw's series of 359 cases from Great Ormond Street Hospital, the lesion was in the duodenum: of these duodenal cases, in 30% the atresia was proximal to the ampulla of Vater and therefore showed no bile-staining of the vomit.

Passage of meconium.—Sticky green meconium should normally be passed in the first twenty-four hours of life. By seventy-two hours, this is replaced by small brownish-yellow motions. Normal yellow semi-formed motions are seen at the end of one week, if normally fed. In Louw's series, 33% and 40% of babies respectively with intestinal or duodenal atresia passed meconium.

In Hirschsprung's disease and in meconium ileus, no meconium may be passed. Thus the presence or absence of meconium in the first seventy-two hours of life does not differentiate between partial and complete obstruction. Further, passage of meconium in the first three days of life does not rule out an intestinal obstruction.

Abdominal gaseous distension.—Normally, the abdomen is often rather protuberant in newborn infants—thus moderate distension is easily overlooked. In 50% of cases with

duodenal atresia in Louw's series, the abdomen appeared to be normal on clinical examination. In 50% of cases of intestinal obstruction, distension was only moderate and less than 30% showed visible peristalsis.

There are thus many exceptions to hypothetical rules for the assessment of obstructive states by clinical examination and firm radiological help can be given in a substantial proportion of cases.

The normal appearances in the alimentary tract.—Swallowed air will be seen in the stomach within five to ten minutes of birth, in the jejunum and ileum within two hours, in the proximal colon within three to four and in the distal colon within six to eight hours.

Hajdu emphasizes that "at twelve hours the whole intestine should be clearly visible by virtue of its gas content and should fill the whole space available in the abdominal cavity. Any departure from this rule will raise the suspicion of intestinal obstruction on the one hand and of a space-occupying lesion on the other".

I suggest that this is rather too strongly emphasized and that the acceptance of this dictum will sometimes lead to an unjustified diagnosis or suspicion of distal obstruction when none is present. The distal colon and rectum are often without a gas content in normal cases, even on repeated examination.

Macnab states that "... the small intestine in the neonate always appears to be dilated", rather implying that we cannot rely on an assessment of the small gut calibre to distinguish between a normal state and a pathologically dilated state. I admit that there is much less difference in the relative calibre of small gut and colon in the infant in comparison with the adult, making a firm distinction as to what is ileum and what is colon in a particular radiograph sometimes very difficult. He states further that "... obstruction of the small intestine cannot be diagnosed unless fluid levels are seen in addition to distended coils of small bowel. The bowel requires to be grossly distended before a fluid level can be seen. ..."

One cannot wholly agree with these specific opinions: firstly, in that I believe it is often possible to distinguish between pathological dilatation of the small gut and its normal state, even in the absence of fluid levels. Secondly, I am sure that fluid levels can be observed before dilatation of the gut reaches more than a moderate degree. It may well depend on the duration of the obstruction and thus on its nature.

Table III gives statistics from Louw's (1952) much-quoted series from Great Ormond Street Hospital—359 cases from 1926 to 1951.

TABLE III.—NEONATAL OBSTRUCTIONS

Œsophageal occlusions			52
Intestinal obstructions 222	Intrinsic 104	Atresias and stenoses	79
		Meconium ileus	13
		Neonatal Hirschsprung's	12
	Extrinsic 118	Volvulus, mesenteric malformations	62
		Intussusception	4
		Diaphragmatic hernia	9
		Inguinal hernia—strangulated	17
		Internal hernia	4
		Exomphalos with obstruction	4
		Miscellaneous	18
Ano-rectal malformations requiring urgent surgery			85

Acknowledgments.—In conclusion, I would like to acknowledge my indebtedness to many colleagues; to all those at Queen Charlotte's Hospital whose work, interest and advice has made this Address possible; to Dr. A. W. Franklin and Dr. A. P. Norman, the Consultant Pædiatricians; to Dr. A. E. Claireaux, the Pathologist; to some of the past Resident Pædiatric Officers, especially Miss M. Taylor, Miss M. M. Ashforth and Miss J. Forsyth; to Miss P. M. Jacobson, the Medical Records Officer and, above all, to Miss A. E. Madden, the Radiographer-in-Charge.

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JOINT MEETING No. 4

Section of Radiology with Section of Ophthalmology

Chairman—E. ROHAN WILLIAMS, M.D., F.R.C.P., F.F.R., D.M.R E.
(President of the Section of Radiology)

[*February* 17, 1956]

DISCUSSION ON ORBITAL TUMOURS

Mr. A. G. Cross: *Surgical Aspects of Orbital Tumours.*

The bony orbit forms a protective structure for the eyeball, which lies within it, and this cavity contains also the optic nerve, the oculomotor muscles, with the nerves and blood vessels which supply them, and the lacrimal gland. It forms a part of the facial structure; it is surrounded by the accessory air sinuses of the nose and it is in close proximity to the brain. Tumours of this region which may be benign or malignant are not frequent in occurrence, and they may arise primarily in the orbit or they may invade it from one of the surrounding structures. The majority of patients with orbital tumours attend first in the ophthalmic department, but other departments are usually requested to assist in diagnosis, and the department which is most frequently consulted is the department of diagnostic radiology, since it has been suggested that nearly 50% of orbital tumours can be absolutely diagnosed by radiological methods. Many orbital tumours can be removed completely by surgery but others—and especially those malignant tumours involving the orbital walls—cannot be so eradicated and radiotherapy is necessary to prevent extension of the growth.

It is proposed to indicate a classification of orbital tumours, to discuss the principles of surgical treatment, and to describe the prognosis following treatment of the various types of tumour by surgical means.

ORBITAL TUMOURS

(1) *Tumours Arising in the Eyeball and Invading the Orbit:*
- (*a*) Malignant melanoma.
- (*b*) Retinoblastoma.

(2) *Tumours of the Orbital Contents:*
- (i) *Benign:*
  - (*a*) Dermoid cyst.
  - (*b*) Angioma.
  - (*c*) Varix.
  - (*d*) Neurofibroma.
  - (*e*) Lipoma, myxoma, etc.
- (ii) *Malignant:*
  - (*a*) Carcinoma of lacrimal gland—mixed tumour.
  - (*b*) Sarcoma: including rhabdomyosarcoma.
  - (*c*) Glioma of optic nerve.
  - (*d*) Endothelioma of optic nerve.
  - (*e*) Hæmopoietic tumours: lymphoma.

(3) *Tumours Arising from Orbital Walls and Nasal Sinuses:*
- (i) *Benign:*
  - (*a*) Osteoma.
  - (*b*) Fibroma.
  - (*c*) Chondroma.
- (ii) *Malignant:*
  - (*a*) Sarcoma of osteogenic periosteum.
  - (*b*) Carcinoma of nasal sinuses.
  - (*c*) Mixed tumours of maxilla.
  - (*d*) Carcinoma and sarcoma of nasopharynx.
  - (*e*) Malignant granuloma.

(4) *Other Secondary Tumours of the Orbit:*
- (*a*) Tumours extending from the cranium.
- (*b*) Metastases.

(1) *Tumours Arising in the Eyeball and Invading the Orbit*

These tumours, the malignant melanoma and retinoblastoma, are removed by enucleation of the eyeball, and in favourable cases this will eradicate the malignant disease. It is true that, in the case of *malignant melanomata*, it is impossible to be confident of cure until a very long period has elapsed, since general dissemination has been reported fifteen and even twenty years after removal of the primary growth, with complete absence of symptoms and signs during the intervening period. A proportion of patients who have had the eyeball removed for malignant melanoma develop secondary deposits in the orbit. This is the result of a direct spread of the growth through the sclera before removal of the eye. This extension may be observed with the naked eye, but frequently can be observed only by histological examination. Invasion through the sclera exercises a decisive influence upon the prognosis of malignant melanoma of the choroid. General dissemination is much more rapid in these cases, and it frequently leads to death within eighteen months. Exenteration of the orbit, accompanied by radiotherapy, may palliate the local condition without influencing the general spread.

Retinoblastoma usually spreads along the optic nerve. Removal of eyes containing this growth must be accompanied by as much optic nerve as possible, and histological examination of the optic nerve is necessary to determine whether the tumour has spread centrally

beyond the point of excision. Such spread necessitates exploration of the orbit through its roof, and removal of the nerve back to the chiasma. Patients who come under treatment late in the course of a retinoblastoma, may show spread of the growth through the sclera and there may also be spread to the regional lymph glands. Such cases must be rare in this country, and treatment can only be palliative.

(2) *Tumours of the Orbital Contents*

Benign tumours which are increasing in size may be removed, and the results are usually satisfactory though damage may occur to the optic nerve or to its blood supply, or to one or more of the oculomotor muscles.

Benign tumours grow slowly and cause relatively little damage to the orbital contents, though pressure on the optic nerve may cause atrophy and a permanent defect of the visual field. Displacement of the orbital contents by a benign tumour usually recovers rapidly after its removal.

The surgical approach may be:

(*a*) Anterior, following a skin incision through one of the eyelids or through the skin of the side of the nose.

(*b*) Lateral, by the method of Krönlein.

(*c*) Superior, by a frontal osteoplastic bone flap, and transcranial extradural approach, or by the method of Dickson Wright.

(*a*) *Anterior approach.* An incision is made through the skin and the orbicularis muscle to expose the periosteum at the orbital margin. The orbital contents are retracted, and the tumour removed. This approach may be extraperiosteal between bone and periosteum, or between periosteum and the orbital contents.

(*b*) *Lateral approach.* The lateral wall of the orbit is exposed and a bone flap is removed. It is triangular in shape, having as its base the lateral margin of the orbit, and as its apex the anterior end of the inferior orbital fissure. This allows effective exploration of the anterior two-thirds of the orbit.

(*c*) *Superior approach.* (i) *Frontal osteoplastic bone flap.* The frontal bone flap is raised and the dura is separated back from the roof of the orbit. This bone is removed, and the orbit can be explored as far back as its apex. The roof of the optic foramen can, if necessary, be removed so that the optic nerve can be exposed back to the optic chiasma.

(ii) *Dickson Wright method.* The outer wall of the lateral wall of the orbit is cleaned by elevating the temporal muscle and a spatula is passed into the orbit, from the front, between the orbital contents and the bone. The outer wall of the orbit is nibbled through behind the orbital margin, so that the orbital contents can be palpated. Then the anterior cranial fossa is opened, and the roof of the orbit is removed. A portion of the orbital margin is removed to allow complete removal of the tumour, and this is subsequently replaced, and fixed in position either by periosteal sutures or by sutures through holes drilled in the bone.

The approach employed depends upon the position of the tumour, and—to some extent—upon the inclination of the surgeon. The superior approach gives the better exposure in a majority of cases, but some damage to the levator palpebræ superioris may occur with resultant ptosis. Tumours in the anterior outer part of the orbit are more conveniently approached by Krönlein's method.

Malignant tumours of the orbital contents can also be removed in some cases by one of these surgical methods. The gliomata and endotheliomata of the optic nerve in particular, which are only locally malignant, can be excised with satisfactory results, and with conservation of the eyeball (Jackson, 1951)—though the vision of the eye is lost. Gliomata of the optic nerve may lie far back in the orbit, and may extend to the chiasma, and therefore a superior approach is preferable. The so-called "mixed" tumours of the lacrimal gland appear to commence in fairly benign form, but may, after a recurrence, assume malignant characteristics and they may cause death by dissemination. These tumours may commence in the orbit independent of the lacrimal gland, presumably in gland nests. Dickson Wright has stated in a personal communication that it is his opinion that section of the capsule of the lacrimal gland before the operation for complete removal of the tumour is to be avoided, and therefore that an anterior approach is undesirable. After a superior approach, this tumour can be lifted from the orbit, and he tells me that after such a removal he has not known a recurrence. The primary malignant tumours of the lacrimal gland, which can be diagnosed by the steady painless enlargement of the gland, cannot usually be properly treated by local removal. Exenteration of the orbit is required, at least, but even this mutilating operation does not usually result in complete eradication of the tumour, and metastases form rapidly. Radiotherapy may be used in some of these cases in association with exenteration, and more radical removal of the orbital walls may have to be considered. Hæmopoietic tumours which may or may not be associated with changes in the blood picture are not suitable for surgical treatment.

(3) *Tumours Arising from the Orbital Walls and from the Nasal Sinuses*

The benign tumours are osteomata, fibromata or chondromata. The osteomata are of the ivory or cancellous type, and they progress very slowly. They may cause proptosis or displacement of the eyeball, but they grow so slowly that diplopia is a rare symptom. Some cause obstruction of the naso-frontal duct, and some may extend to the meninges and cause brain abscess and meningitis. These tumours can be removed, and the approach depends upon the position of the tumour and upon the technique of the surgeon. Many of them are removed by Ear, Nose and Throat surgeons, together with a portion of the maxilla or frontal bone, usually by the anterior approach. Howells and Jones (1954) have reported fifteen cases of this type, all of which were removed, most through the external frontal sinus operation incision.

The malignant tumours arising from the orbital walls also are frequently treated by the Ear, Nose and Throat surgeons. Many of them originate in the antrum and ethmoidal sinuses. Primary tumours of the frontal sinus are unknown, but metastases may occur there and invade the orbit. Generally speaking, all these tumours are treated by surgical treatment of a radical type, involving fenestration of the hard palate and removal of a varying amount of the maxilla and ethmoids, but radiotherapy is always necessary as an associated treatment. Patients with malignant tumours of the nasopharynx sometimes appear first in the ophthalmic department. The growth is symptomless in its early stages, and invasion of the orbit to cause proptosis or of the base of the skull to cause palsy of the extrinsic ocular muscles, may be its first manifestation. Treatment is largely in the hands of the radiotherapists.

Howells (1953) has described the treatment of a number of malignant tumours of that region which he has called the naso-orbital frontier, all of them by radical removal and radiotherapy. One case of adenocarcinoma of the lacrimal gland survived two and a half years, and a second after exenteration and radiotherapy was still well after one year. A fibrosarcoma of the orbital wall had not recurred. An oat cell carcinoma of the frontal sinus, metastatic in type though the primary was never found, and cases of tumours of the ethmoid and antrum were recorded.

A few words should be said about that pathological condition which appears in the nose, and which is called a malignant granuloma. It may spread to the orbit. It appears to have some analogy to the Mooren's ulcer of the cornea in that it behaves as a malignant tumour, and may be benefited by radiotherapy, but shows the histological features of a chronic inflammatory process.

(4) *Other Secondary Tumours of the Orbit*

The orbit may be involved in the extension of malignant tumours from within the cranial cavity, usually through the optic foramen. Sometimes diagnosed in the ophthalmic department, the surgical treatment of such tumours is in the hands of the neurosurgeon. Metastases may occasionally appear in the orbit, following primary tumours of the breast, lungs and other organs. Hutchinson's tumour (neuroblastoma) occurs in young children. Surgical treatment is rarely indicated, but they may be helped by radiotherapy.

Pseudotumour of the orbit should be considered separately. This is a fibrosis within the orbit which may or may not be circumscribed, and which gives rise to proptosis. It appears that there is no constant ætiology. Removal has been described, but this may cause considerable destruction of the orbital contents, and conservative treatment is indicated when possible. Decompression of the orbit—by the method of Naffzigger through an osteoplastic frontal flap—may be helpful, and radiotherapy may be employed.

I have said that orbital tumours are not common. Published series of cases have not therefore, as a rule, contained a large number. Foster (1955) has described 52 cases, Black (1954) 20 cases, Wild (1950) 31 cases, Mussini-Montpellier and Garchon (1950) 44 cases, and Hamilton (1952) 46 cases.

The following series is composed of personal cases together with those treated at the Atkinson Morley Hospital during the past ten years, and at the Royal National Throat, Nose and Ear Hospital during the past five years, and I am grateful to Mr. Wylie McKissock, and to Professor F. C. Ormerod and the Staff of the Royal National Throat, Nose and Ear Hospital for their permission to record them.

These cases indicate that benign tumours of the orbit can be excised with satisfactory results, and that some of the less active of the malignant tumours can similarly be removed with good prospects of cure. Malignant orbital tumours which invade from the eyeball, the nasal sinuses, or the nasopharynx, have a bad prognosis, since the disease has usually reached an advanced state. Exenteration is sometimes carried out in these cases, but its value is doubtful. Rendahl (1952) followed up 23 cases of exenteration, and traced 15 cases. He discovered that 14 had died in an average of two years after the operation. It may be that radiotherapy can help the patient as much as exenteration, and that only in the cases of radio-resistance is this mutilating operation required.

CASES OF ORBITAL TUMOUR

Tumours of Orbital Contents:
Benign 7 cases.
Dermoid cyst:
3 cases. Satisfactory removal.
Residual diplopia in all three.
Angioma:
1 case. Satisfactory removal.
Neurofibroma:
1 case. Satisfactory removal.
Lipoma:
1 case. Satisfactory removal.
Simple cyst:
1 case. Satisfactory removal.
Malignant 12 cases.
Carcinoma of lacrimal gland 4 cases.
1 died from metastases in spite of exenteration, and radiotherapy.
3 satisfactory after removal, but 1 died of poliomyelitis.
Glioma of optic nerve 3 cases.
2 removed. 1 satisfactory; 1 invaded the other optic nerve through the chiasma.
1 inoperable. Treated with radiotherapy.
Fibrosarcoma 3 cases.
1 exenteration: satisfactory.
1 exenteration and radiotherapy: deteriorating.
1 radiotherapy: satisfactory.
Lymphatic leukæmia 1 case.
Died in 1 year.
Lymphoma 1 case.
Satisfactory with radiotherapy.

Tumours Arising from Orbital Walls:
Benign 6 cases.
Osteoma:
2 cases. 1 removed: satisfactory.
1 not removed due to small disability.
Fibroma:
3 cases. Removed: satisfactory.
Chondroma:
1 case. Removed: untraced.
Malignant 17 cases.
Carcinoma of antrum 11 cases.
5 died.
6 survived up to five years. (One after exenteration of orbit and removal of maxilla.)
Carcinoma of ethmoids 3 cases.
All died.
Lymphosarcoma of ethmoids 1 case.
Satisfactory with radiotherapy.
Malignant granuloma 2 cases.
Both deteriorating: 1 exenteration.

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Mr. J. W. Cowie: *Opaque Media in the Investigation of Orbital Tumours.*

In the investigation of orbital tumours radiology up to the present time has been of limited value. Plain films give little information unless the bony wall of the orbit is affected, by expansion, erosion or sclerosis, or alternatively, areas adjacent to the orbit may show abnormalities suggesting a primary cause for the orbital pathology. This is notably true of the paranasal sinuses.

As in many other radiological fields, satisfactory investigation of a soft tissue area must involve the use of contrast media by extravascular or intravascular administration, and brief consideration will be given to the different methods which have been used.

Arteriography and venography have been applied to this problem but the results have proved very disappointing, perhaps due to the fact that the retrobulbar tissues are relatively avascular and the vessels involved small in calibre.

Extravascular injection methods have shown greater promise and a variety of media have been used.

Air injection with or without tomography has been employed, notably by Offret who has succeeded in showing orbital tumours but the method is lacking in precision and the volumes of air employed cause discomfort and are slowly absorbed.

Oily solutions permeate unevenly and give films difficult to interpret. They also act as a long-term irritant.

Water soluble media. Of these a large number is now available of which the best known is diodone. Diodone has a very good safety record in radiological work and a wide fund of experience of its extravascular injection is available. A very few cases of tissue damage

have been recorded and up to the present time these have all followed injection of medium at a concentration of 35% or higher.

In the development of the technique used at Leeds Mr. Groves and myself (Groves and Cowie, 1955) attempted first of all to determine by experimental injection in the cadaver the lowest concentration of diodone which would produce satisfactory radiographs on injection of the orbital tissue planes. This we found to be 17½% and in clinical use this is obtained by mixing equal quantities of 4% Novocain and 35% diodone.

We found that the three separate tissue planes of the orbit could be injected individually and that each produced a characteristic radiographic appearance.

(1) The Tenon's capsule will contain 1·5 to 2 c.c. and produces a crescent appearance in the lateral projection and an ill-defined circular opacity in the P.A. view.

(2) The outer surgical space (Duke-Elder, 1954) may be usefully injected only in quadrants as otherwise the appearances become confused due to overlap. The space appears large since the medium readily compresses the muscle cone.

(3) The central surgical space (Duke-Elder, 1954) is best shown by an injection of 3–4 c.c. given as for block of the ciliary ganglion. The appearances obtained are worthy of some comment since injections of this type have been used in all cases of orbital space-occupying lesions investigated by us.

In the postero-anterior view the opacity resembles an irregular four-leaf clover and we believe that the extra-ocular muscles lie in the indentations between the "leaves" and give rise to this pattern by resisting the expansion of the contents of the cone while the intermuscular fascia balloons. It follows that a small injection will give rise to smaller "leaves" and this must be borne in mind in use of the technique.

In the lateral view the term muscle cone describes the appearance adequately and the quantities used give a cone with slightly concave sides. Quantities greater than 4 c.c. tend to rupture into the outer surgical space and occupy the narrow area usually seen between the cone and the bony orbit.

The muscle cone will be seen "face on" in the optic foramen or orbital axis projection and in the straight postero-anterior view there is some tendency for the gap between the medium and the lateral orbital wall to appear greater than that on the medial side.

In order to assess the distortion of normal patterns caused by space-occupying lesions of known size warm cocoa butter, which rapidly solidifies in the cadaver, was injected. By dissection it was confirmed that it assumed a relatively compact shape. Diodone was then injected into the fascial space occupied by the tumour or the adjacent one. To identify the tumour radiologically barium powder was mixed with the cocoa butter and demonstrated the displacement and distortion of the cone by a tumour above the cone.

A mass in the central surgical space followed by an injection of diodone into the same area showed ballooning and abnormality of the normal patterns.

A large series of such experiments was carried out to investigate the different forms of distortion to be expected with varying sites of tumour.

Having established the feasibility of this procedure in the cadaver we next desired to test its safety in clinical use. Katz and Ledoux (1935) have used this medium to measure the length of the eye and Pettinati (1953) to localize foreign bodies and neither publication records any untoward effects. Injections were given by us to four patients awaiting enucleation. No pain was experienced on injection but after an interval of one hour—a period consistent with the action of the local anæsthetic—the patients suffered a dull ache behind the eye for five to six hours. This was readily controlled by mild analgesics. At operation within 24 hours the tissues appeared normal, orbital implants were inserted and worked satisfactorily.

This encouraged us to subject the method to prolonged clinical trial and up to the present time in the investigation of foreign bodies and space-occupying lesions a total of 15 patients have been submitted to the procedure being given in all a total of 18 injections. No complications have arisen apart from the development of retro-orbital hæmatoma in one or two cases.

Manchester records the experience of himself and his co-workers using diodone injections to the orbit in rabbits and human beings (Manchester, 1953; Manchester *et al.* 1955). He has encountered serious complications including retinal artery spasm and necrosis of the sclera. These complications are, happily, outside our experience in Leeds, and we attribute this to the fact that the technique employed by Manchester involves the use of 35% diodone in quantities substantially greater (5–6 c.c.) than those employed by us.

Up to the present time ten cases of orbital space-occupying lesion have been investigated by the method described and are available for assessment.

In 6 cases the presence and site of a mass was demonstrated and has since been confirmed by operation.

In 2 cases a mass was shown but no operation was indicated.

In 1 case the findings were considered equivocal and there is no present clinical indication for operation. This examination may be repeated at a later date.

In 1 case orbital varices have been diagnosed clinically and the muscle cone pattern shown to be normal in outline, but a little large and mottled. This is considered to be a reasonable finding in such a case.

Detailed cases were then presented with radiographs.

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Dr. M. Lederman (Radiotherapy Department, The Royal Marsden Hospital): *Radiation Treatment of Orbital Tumours*

Table I shows the material seen at the Royal Marsden Hospital. This is a selected material since patients are sent chiefly for radiotherapy and cannot therefore be used for assessing the incidence of orbital neoplasms.

The hæmangioma was the commonest of the benign orbital tumours seen (8 cases) and radiotherapy is almost certainly the treatment method of choice.

The primary tumours seen by the radiotherapist are those the surgeon regards as unsuitable for operation, i.e. sarcomata of lymphoid tissue, other rapidly growing sarcomata of children and young adults, and malignant lacrimal gland tumours when total removal of the tumour cannot be achieved (Table II).

TABLE I.—MATERIAL SEEN AT THE ROYAL MARSDEN HOSPITAL 1933–1955

Benign tumours	17
Granulomata	5
Primary malignant tumours	42
Secondary malignant tumours	126
Total	190

TABLE II.—PRIMARY MALIGNANT TUMOURS

Sarcomata of lymphoid tissue		14
(1) "Benign" lymphoma	6	
(2) Lymphosarcoma	7	
(3) Reticulosarcoma	1	
Rhabdomyosarcoma		7
Other sarcomata		6
Lacrimal gland tumours		14
Nerve tissue tumours		
Glioma of the optic nerve		1
Total		42

The sarcomata of lymphoid tissue are the commonest primary orbital tumours seen; they are all uniformly radiosensitive and radiotherapy is undoubtedly the treatment of choice. There is a wide variation in structure and behaviour of these tumours, for the histologically benign lymphoma may cause rapid death from dissemination whereas the patient with a lymphosarcoma may survive for many years. The reticulosarcoma is the least malignant of the group whereas of the lymphosarcomata and benign lymphomata some cases may disseminate widely or develop a leukæmic blood picture whilst others remain well for varying periods. In this series of 14 cases, two of the "benign" lymphomata developed secondary manifestations (chest, spine) and one patient developed leukæmia. The two bilateral lymphomata both presented laryngeal deposits (bilateral false cord infiltration and a single deposit on the aryepiglottic fold). It would appear wise to examine the larynx routinely in all cases of orbital lymphomata.

The results (Table III) clearly show that the prognosis for this group of tumours is reasonably good and the eye should prove no problem as the only risk of damage is late cataract.

TABLE III

	Number treated	Age	Sex	Side	Survival 5 yr.	Survival 3 yr.
Lymphoma	6	40–79 yrs. average 53 yrs.	3 M. 3 F.	0 R. 4 L. 2 bilateral	1/2	5/5
Lymphosarcoma	7	47–82 yrs. average 64 yrs.	4 M. 3 F.	2 R. 4 L.	3/3	4/6
Reticulosarcoma	1	53 yrs.	M	R	Alive for 13 yrs.	

The Rhabdomyosarcomata

Our experience of this rare tumour has been limited to 7 orbital and 4 extra-orbital cases. Sections have been available for all the orbital cases and in 3, the presence of striations has been demonstrated. In the remainder where this was not so the clinical features and typical course of the disease and its response to radiation have in our view justified the diagnosis.

The characteristics of the orbital rhabdomyosarcoma in this series are:

(1) they mostly occur in children,
(2) they usually remain localized to the orbit,
(3) they are highly radiosensitive but only exceptionally radiocurable since prompt recurrence is nearly always the rule.

The eldest two patients in the series have alone survived without loss of the eye, although one patient has developed xerophthalmia and has little vision in the eye. The longest survivor has evidence of a radiation cataract. The third survivor, aged 6, is so far free of recurrence for three months (Table IV).

TABLE IV.—RHABDOMYOSARCOMA

Number	7
Age	3–26 years
Sex	2 M. 5 F.
Side	5 R. 2 L.
Histologically proven	3 Rhabdomyosarcoma
	3 Sarcoma, suggestive of rhabdomyosarcoma
	1 Undifferentiated sarcoma
Survivors	1 for 3 years (*æt* 19)—proven
	1 for 1½ years (*æt* 26)—suggestive
	1 for 3 mths. (*æt* 6)—undiff. sarc.

The rhabdomyosarcoma should always be treated by radiotherapy in the first instance, as all these tumours disappear under radiation, many only to recur promptly in which event exenteration can be performed. There is no evidence to show that immediate exenteration has any advantage for cases behaving in this particular fashion and, as these tumours appear to remain localized, any delay in operation because of the preliminary attempt at cure by radiotherapy is not apparently associated with an increased risk of metastases. In the 4 patients dying of their disease, distant metastases were not demonstrated but post-mortem examinations were not obtained. Distant metastases did occur, however, in the extra-orbital group which also proved less responsive to radiation.

Lacrimal Gland Tumours

Tumours of the lacrimal gland are rare, the commonest tumour occurring being the "mixed" tumour which appears to be analogous both clinically and histologically to the mixed tumour affecting the major and minor salivary glands of the buccal cavity and pharynx. These tumours have a common epithelial origin but because of their cellular pleomorphism the histological appearances may range from the benign adenoma to the adenocarcinoma or, on occasion, a tumour may be completely anaplastic. These wide variations in morphology are reflected in their clinical behaviour which may vary from apparent simplicity to high malignancy with widespread metastases. However benign the histological picture, these tumours should always be regarded clinically as malignant, and because of their slow remorseless progress cure by any method of treatment cannot be judged in terms of the ordinary three- or five-year survival rates.

TABLE V.—LACRIMAL GLAND TUMOURS

	No.	Age	Sex	Side	Removal of eye Pre-radiation	Removal of eye Post-radiation	Survival 5 yr.	Survival 3 yr.
Mixed tumour ..	5	37–76 yrs. average 53 yrs.	3 M. 2 F.	2 R. 3 L.	2	—	2/3	3/4
Adenocarcinoma	4	36–52 yrs. average 46 yrs.	1 M. 3 F.	0 R. 4 L.	3	—	2/3	3/4
Undifferentiated carcinoma	3	31–65 yrs. average 43 yrs.	1 M. 2 F.	1 R. 2 L.	1	—	1/2	1/2
Lymphosarcoma	2	49 and 59 yrs. average 54 yrs.	1 M. 1 F.	0 R. 1 L. 1 bilat'l.	—	—	0/1	1/2

Mixed salivary tumours are relatively radioresistant but radiotherapy can help reduce the recurrence rate within the limitations and fallacies imposed by the five-year period of observation and should therefore be routinely used in association with surgery. Radiotherapy is the method of choice for the inoperable, recurrent or highly malignant epithelial tumours and the lymphosarcomata. Table V shows the results obtained. It can be seen that the adenocarcinoma is by no means as deadly a tumour as is commonly believed.

Secondary Malignant Tumours

Table VI lists the sources from whence the orbit can be invaded secondarily by malignant disease. Among these the commonest and most important cause of secondary invasion of the orbit is spread of cancer from the paranasal sinuses or less commonly from the post-nasal space, the remaining secondary tumours being rarely causes of diagnostic or therapeutic difficulty.

TABLE VI.—SECONDARY MALIGNANT TUMOURS

Spread from:		
(1) Intra-ocular tumours		6
(*a*) Choroidal melanoma	3	
(*b*) Retinoblastoma	3	
(2) Neoplasms arising in neighbouring regions		100
(*a*) Paranasal sinuses	77	
(*b*) Post-nasal space	14	
(*c*) Cranial cavity	1	
(*d*) Lids and epibulbar region	8	
(3) Metastases from:		
(*a*) Ca. breast	3	
(*b*) Ca. bronchus	3	
(*c*) Ca. kidney	2	
(*d*) Neuroblastoma	2	
		10
(4) Orbital manifestations of generalised lymphoid tumours		10
Total		126

Table VII shows the incidence of orbital invasion in a series of such cases seen at the Royal Marsden Hospital. The presence of orbital invasion is always of grave significance as far as prognosis is concerned and adds very considerably to the technical difficulties of treatment because of the need to avoid radiation damage to the eye.

TABLE VII

	Carcinoma antrum Total No. cases 128	Carcinoma ethmoid Total No. cases 44	Carcinoma nasopharynx Total No. cases 165
Orbital invasion	54	23	14
Cranial nerve involvement	17	5	43
Post-radiation complications	15	4	5
Eye removed	5	3	—
Orbit exenterated	6	3	—

I wish to emphasize as my personal view that removal of a sound eye or exenteration of the orbit in the treatment of antral or ethmoidal cancer is never justifiable as a primary measure for its adds little to the patient's chances of survival. The presence of neoplasm in the orbit is an index of the extensive nature of the disease and if radiotherapy is first applied and fails then subsequent surgery is no more likely to be successful. In our total series of 172 cases of antral and ethmoidal carcinoma there were 9 exenterations and only one patient is alive a year later. Of the 8 other patients who lost the eye (in no case was removal necessary because of radiation damage), there are 2 living for more than three years; in both cases the patients came into the hands of plastic surgeons, one eye was removed for infection and the other against advice to the contrary.

In advocating radiotherapy for the treatment of malignant orbital tumours one must be ever conscious of the possible risks of damage to the normal eye. If the risks of radiation damage to the eye are considerable then a case can be made out for removing the eye before embarking upon radiotherapy. If, however, the risks can be shown to be small or otherwise worth while accepting then clearly the eye should be left.

Complete protection of the eye during the irradiation of a malignant orbital tumour cannot be obtained nor is it desirable since tumour tissue may simultaneously be protected: the most one can hope to achieve is to protect from direct radiation the vulnerable ocular tissues forming the anterior segment of the eye, namely the cornea, iris, ciliary body and lens.

The risks of radiation damage to the eye depend on the following factors:

(1) The radiosensitivity of the tumour and the dosage employed.
(2) The state of the eye before treatment.
(3) The technical method of radiation employed.
(4) The degree of protection possible.

Table VIII lists the ocular complications encountered. These are permanent and due to damage by radiation.

TABLE VIII.—ORBITAL TUMOURS
Complications of Radiotherapy

	Tumour	
	Primary	Secondary
Epilation	—	—
Lid scarring and deformity	—	—
Socket contraction	—	—
Chronic conjunctivitis	—	—
Xerophthalmia	1	—
Superficial punctate keratitis	4	3
Corneal ulcer	2	4
Corneal vascularized opacity	—	1
Vitreous hæmorrhages	1	1
Cataract	6 single 1 bilateral	14 single 5 bilateral
Osteonecrosis	—	—

Cataract is by far the commonest single complication encountered and is to be expected in all malignant cases treated. So far we have 20 unilateral and 6 bilateral cataracts. There is usually a latent period of some three years between the treatment and the onset of the cataract which as a rule occasions surprisingly little complaint. Extraction of the cataract has been performed in two cases, apparently without undue difficulty. In my opinion, risk of a radiation cataract is always justifiably taken for the treatment of a malignant eye or orbital lesion where no alternative to radiotherapy exists or where surgical treatment entails loss of the eye.

The remaining complications are encountered exceptionally.

RADIOTHERAPY TECHNIQUE

The technique of treating an orbital tumour depends mainly on whether the eye be present and whether the tumour be primary or secondary or bilateral. If a sound eye be present, no effort must be spared for its protection, whereas if the eye has been removed techniques can be simplified and extended in range. With a primary orbital tumour treatment can be localized to the orbit with consequent limitation in general and local reactions to radiation; where there is secondary invasion of the orbit, particularly from the paranasal sinuses or post-nasal space, the need to irradiate the orbit complicates to a great extent the technique of treatment of the primary site and imposes an extra and often severe burden upon the patient.

Orbital Tumours with Sound Eye Present

Factors influencing the technique of radiotherapy:

(1) *General Factors*

(*a*) *The age and general condition of the patient* do not matter greatly provided the patient is neither too senile nor too young and fractious to co-operate in treatment. Occasionally young children may require rectal paraldehyde at the beginning of treatment but as a rule they quickly learn to co-operate.

(*b*) *The state of the eye.*—It may be stated quite categorically that it should never be necessary to remove a normal eye as a preliminary measure to a course of radiotherapy. Removal of the eye as a preliminary to radiotherapy can be considered if the eye be blind or if a severe exposure or neuroparalytic keratitis be present. Even in these cases, however, removal of the eye is not absolutely necessary and can be left if the patient is averse to its removal.

From the point of view of technique, proptosis and chemosis are always a problem especially when associated with a squamous carcinoma of the paranasal sinuses or post-nasal space. In these cases, neoplastic invasion of the orbital bones is always present in association with sepsis and the presence of a "malignant osteitis" usually precludes a successful outcome to radiation treatment unless the affected bone can be surgically removed.

(*c*) *The purpose of treatment.*—Whenever curative treatment is undertaken every effort must be made to limit the permanent damage inflicted on the eye; but with palliative treatment the whole globe should always be protected from direct irradiation and reactions minimized as much as possible by control of dosage. The purpose of treatment in these cases is to reduce pain and proptosis if possible so as to enable the patient to die without having to undergo an operation on the eye or to endure the miseries of a progressive exposure keratitis.

(2) *Local Factors*

Of the local factors affecting technique the chief are the nature and extent of the tumour and its situation within the orbit.

(*a*) *Benign tumours and granulomata.*—When the tumour is restricted to one part of the orbit radiation can be localized to the affected region. Treatment can be given through a single anterior field applied directly to the eye with some form of protection to be described later. The eye should be completely protected and no risk of damage should be taken. Safety should also be sought in the use of the lowest possible radiation dosage, i.e. 50–100 r weekly to the granulomata for 4–6 weeks, a single dose of 200–400 r for the angiomata repeated no more than twice in the course of a year or eighteen months, and 2,000 r in one month for the nerve sheath tumours.

(*b*) *Primary malignant tumours.*—When dealing with these tumours, the technique of treatment must be such that the whole orbit is irradiated. There are only two exceptions to this rule:

(i) the pre- or post-operative treatment of a "mixed" tumour of the lacrimal gland when treatment can be localized to the region of the lacrimal fossa, care being taken to irradiate a wide zone of the surrounding bone because of the known tendency of these tumours to produce early and wide bone invasion.

(ii) In the treatment of glioma of the optic nerve radiation can be largely concentrated in the retro-ocular segment of the orbit, the posterior part of the globe related to the nerve head alone being included in the field of radiation.

In treating a primary orbital tumour two fields (an anterior and a lateral) are usually necessary although very occasionally a single direct field can be employed for some of the very sensitive sarcomas of lymphoid tissue. The field sizes used are 4×4 sq. cm. minimum, the exact size depending on the extent of the tumour, and for purposes of beam direction the fields are mounted on wax seats on a plaster cast if 220 kV X-rays are used or if 2 MeV radiation is employed the fields are outlined on a Perspex cast on which are also mounted the points at which the central axes of the beams emerge. The use of a light device instead of a closed-ended applicator is of particular value since it is atraumatic and is the only technical method of administering radiation which permits the use of the indirect method of eye protection.

Ocular protection may be achieved in two ways, directly or indirectly, depending on the degree of proptosis present and the quality of the radiation employed.

Bilateral Tumours

The rare bilateral tumours of the orbit are usually radiosensitive sarcomas of lymphoid tissue and the technique of treatment should be the same for both orbits, excepting that it is wise to begin treatment on the most seriously affected side and allow a few days' interval before beginning treatment to the second tumour.

Secondary Orbital Tumours

The important secondary orbital tumours are those due to extension of neoplasm from the adjacent paranasal sinuses or post-nasal space. The two cardinal principles to be observed in treating secondary tumours from these regions are: (1) The treatment technique must be predominantly directed towards control of the primary site and the orbital extension coincidently and adequately included within the treatment zone. (2) The treatment can be limited to the part of the orbit affected.

Our basic technique is to irradiate *en bloc* the whole antrum, ethmoid and orbital cavity on the affected side ensuring at the same time protection of both eyes.

In spite of shielding the eye on the affected side from direct irradiation the high dosage used coupled with the high percentage backscatter into the eye may result in a radiation cataract.

In the case of post-nasal tumours, treatment is directed to the post-nasal space unless evidence of spread outside this region can be demonstrated. If the orbit be involved as evidenced by proptosis, an anterior field is added over the affected eye with direct or indirect corneal protection and the whole orbit treated since invasion usually takes place from behind and selective protection of the orbit is unwise.

The Technique of Treating Primary and Secondary Orbital Tumours After Removal of the Eye

After removal of the eye or exenteration of the orbit post-operative treatment may be required as an immediate measure because of doubtful or incomplete surgical removal of all the tumour or because of frank recurrence in the socket or orbital cavity. The absence of the eye simplifies technique of treatment by external irradiation and also permits the use of purely local methods of irradiation by radium applicator or implantation.

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Section of Odontology

President—Professor H. H. STONES, M.D., M.D.S., F.D.S. R.C.S.

[*March* 26, 1956]

Some Observations on Amelogenesis Imperfecta and Calcification of the Dental Enamel

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THE condition of amelogenesis imperfecta had been described under many different names before Weinmann, Svoboda and Woods first introduced this title in 1945. One of the earliest descriptions is that of Spokes who, in 1890, described to the Odontological Society of Great Britain a case of "brown teeth" with a familial history. In 1907 Turner described some cases of hereditary hypoplasia of the teeth in five generations of the same family, but apart from this, little interest was shown in the condition until after 1930. Even to-day the total number of contributions on this subject is small and most of them are reports of one or two cases. The first notable contribution on the subject is a paper by Finn (1938) in which he distinguishes between brown hypoplasia of the enamel and hereditary opalescent dentine. He comments that in brown hypoplasia of the enamel there are no faults in the dentine, a finding which still seems to be generally acceptable. After this, the most important contribution was made by Weinmann, Svoboda and Woods (1945). They described two types of hereditary abnormalities of the enamel, the hypoplastic and the hypocalcified and used the findings in the latter as an important argument in support of the theory of enamel maturation propounded by Diamond and Weinmann (1940).

No satisfactory definition of amelogenesis imperfecta has been found in the literature. While the great majority of recorded cases are hereditary, Wittner (1945), Soifer (1953) and Weyman (1955), have recorded idiopathic cases. From the literature it seems clear that the term implies a generalized fault of enamel structure affecting all the teeth of one or both dentitions. The faults do not seem to be related to any specific period of time during enamel development, nor to any intercurrent disease or dietary abnormality. It may be hereditary or may occur spontaneously in one or more members of a family.

Of the 21 cases to be discussed, 18 were seen clinically at the Bristol Dental Hospital, one was a case from Mr. R. R. Stephens, who kindly provided a colour photograph and a specimen, one was a case published by Miss J. Weyman (1955), who kindly provided a specimen, and another was published by Professor M. A. Rushton (1950), who kindly loaned the sections for examination. Of the 21 cases, 9 are clearly hereditary and are derived from six families. In one family the condition can be traced through seven generations. Of the remaining 12 cases, 2 are probably hereditary, 6 appear to be idiopathic and in 4 cases no family history was available. In 9 cases where the deciduous teeth were seen they were affected. The permanent teeth were seen to be affected in twenty cases, and in 8 cases where both dentitions were seen, both were affected.

This report is concerned chiefly with clinical findings and the results of soft X-rays of ground sections of the teeth. It is hoped to extend the study to include other investigations later. Radiographic examinations of the skeleton and chemical investigations of the blood were made in 4 cases, but nothing abnormal was found, and as this agreed with the findings in the literature, no further investigations of this kind were undertaken. The cases were classified first on the basis of clinical examination and intra-oral radiography into hypoplastic and non-hypoplastic types. The degree and site of staining and chipping were also recorded. Representative teeth which had been obtained as specimens, including erupted, unerupted deciduous and permanent teeth where possible, were then sectioned bucco-lingually and ground down to a thickness of approximately 0·005 in. These sections were then X-rayed by the technique described by Darling and Crabb (1956). The cases were then reclassified according to the distribution of the hypocalcification demonstrated.

In general the two classifications seem to correspond very well in that the same faults in structure were found in all the cases in each clinical group, with few reservations.

The hypoplastic cases fell naturally into three groups: Those with generalized pitting of the enamel—group 1, 3 cases from three families (Fig. 1A). Those with vertical grooving combined with wrinkling of the enamel surface—group 2, 3 cases from two families (Fig. 2A).

Those with a marked deficiency in the thickness of the enamel—group 3, 4 cases from three families (Fig. 3A). This last type was associated with discoloration and chipping of the enamel, and radiographs showed resorption of unerupted teeth in 2 cases. The grouping seems to correspond with the types of cases found in the literature. Weyman (1955) described a case of pitting, Spokes (1890) a case of vertical grooving, while Weinmann, Svoboda and Woods (1945) and Rushton (1950) have described cases with reduced thickness of the enamel.

The remaining cases were presumed to be of the hypocalcified variety and these were divided first on the basis of the distribution of chipping and staining. It was found that in most of the cases the whole of the enamel of each tooth was affected but in 3 cases the lesions were localized to one area of the enamel, occurring in each tooth at the same site (Fig. 6A). These were placed together in group 5. The other cases were classified on the basis of the degree of staining and chipping found and on the texture of the enamel. Staining varied from yellow to a very dark brown and in each case the staining was accompanied by opacity of the enamel. The texture of the enamel was arbitrarily described as hard, chalky or cheesy, while the chipping was described as moderate or gross. None of these is a very reliable index in itself but it was found that two fairly clear groups existed. The first group (group 4A) consisted of 3 cases from three families in which there was little chipping of the enamel, which was chalky, or not as hard as normal. There was only moderate staining which varied between yellow and light brown (Fig. 4A). The second group (group 4B) consisted of 5 cases from four families, in which the enamel was very badly stained and chipped, often seeming to be almost absent except at the cervical margins where usually a shoulder of enamel remained (Fig. 5A). In these cases the enamel was soft or cheesy on recently erupted teeth, but even on badly chipped teeth a thin layer of hard enamel was usually found adhering to the dentine. In one case which conformed in all other respects there were some transverse grooves on the labial surfaces of the maxillary central incisors, suggesting hypoplasia. It was not seen on other teeth, and in view of the other findings it was ignored for purposes of classification.

In general, clinical radiographs supported the clinical findings and there was a reduced radiopacity of the enamel in the cases of presumed hypocalcification.

Specimens were obtained from 15 of the 21 cases, including those loaned. The specimens came from 2 cases in group 1, 2 cases in group 2, 4 cases in group 3, 2 cases in group 4A, 4 cases in group 4B and 1 case in group 5. Wherever possible the specimens from a case were divided into two groups. One group was sectioned and radiographed while the other group was retained for further study.

The findings from unerupted teeth were viewed with caution, but it was found that in all cases where they were used they confirmed the faults found in erupted teeth.

The soft X-rays of the sections were examined macroscopically and microscopically. All the faults described were visible to the naked eye. No quantitative estimates of the degree of hypocalcification have yet been made so that although it is thought that in nearly all the cases of groups 3 and 4 the enamel appears to be generally hypocalcified, this has not in fact been established.

In three erupted teeth from 2 cases from two families in group 1 no evidence of hypocalcification was found (Fig. 1B). In two teeth from one case in group 2 it was found that there was a zone of markedly hypocalcified enamel extending outward from the amelodentinal junction for about one-third of the thickness of the enamel (Fig. 2B). The outer margin of this zone ran roughly parallel to the enamel surface. Two teeth from one other case in this group showed a similar but broader zone of hypocalcification, possibly related to the striæ of Retzius at one point.

In twelve teeth from 4 cases in two families in group 3, the enamel was much thinner than normal and showed a zone of hypocalcification lying midway between the amelodentinal junction and the enamel surface (Fig. 3B). It varied in width and degree of hypocalcification and is probably best described as involving the middle zone of the width of the enamel. In one tooth from Professor Rushton's case which was assigned to this group on clinical evidence, the enamel was very thin, but no zone of hypocalcification within the enamel has yet been demonstrated. This may be due to technical difficulties.

In eight teeth from 2 cases from two families in group 4A, marked hypocalcification was found involving the whole of the enamel except for narrow zones at the surface and at the amelodentinal junction (Fig. 4B). These narrow zones were comparatively well calcified.

In group 4B 22 teeth from 4 cases from three families were examined. The erupted teeth in this group all showed gross loss of enamel, but invariably the dentine was covered by thin remnants of enamel while a shoulder of enamel of full thickness was often found cervically. In these areas and in more recently erupted teeth where more enamel remained, faults were found similar to those in group 4A, but the zones of well-calcified enamel appeared to be much thinner at the enamel surface and rather broader at the amelodentinal junction

FIG. 1A.—Case from group 1 showing generalized pitting of enamel which is otherwise normal to clinical examination.

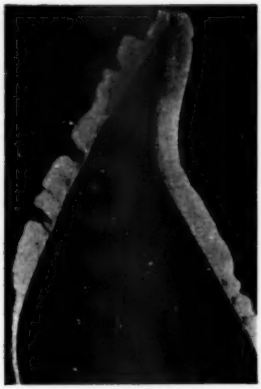

FIG. 1B.—Radiograph (×5) of a ground section of an incisor from the same group showing no evidence of hypocalcification.

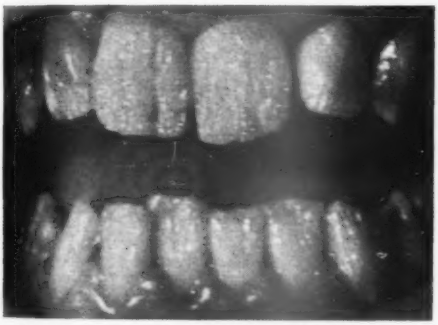

FIG. 2A.—Case from group 2 showing vertical grooves and wrinkling of enamel of all teeth. The enamel is otherwise clinically normal.

FIG. 2B.—Radiograph (×6) of a ground section of a premolar from the same patient showing an inner zone of hypocalcified enamel.

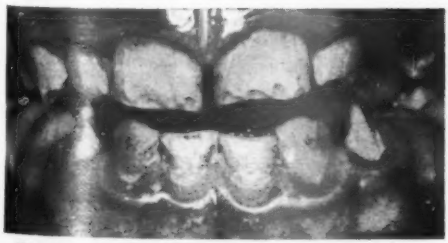

FIG. 3A.—Case from group 3 showing generalized thinness and opacity of enamel with slight chipping and staining.

FIG. 3B.—Radiograph (×6) of a ground section of a deciduous molar from the same patient showing the thin enamel with a broad zone of hypocalcification involving most of the enamel.

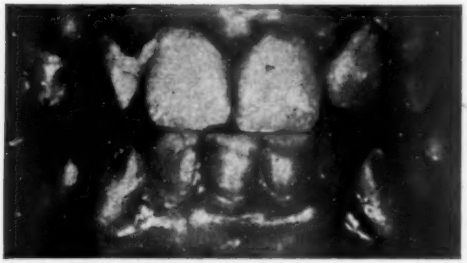

FIG. 4A.—Case from group 4A showing the enamel of normal contour and thickness though opaque and slightly stained.

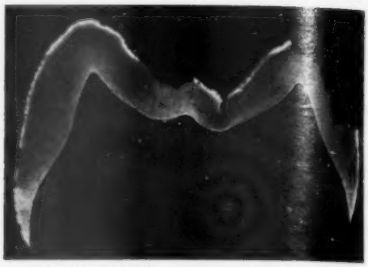

FIG. 4B.—Radiograph (×5) of a ground section of a molar from the same case showing hypocalcification of the enamel except for zones next to the amelodentinal junction and at the enamel surface.

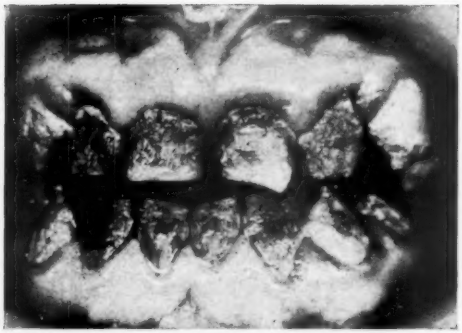

FIG. 5A.—Case from group 4B showing gross loss of the enamel by chipping, with heavy staining of the teeth.

FIG. 5B.—Radiograph (×6) of a ground section of a recently erupted tooth from the same case, showing hypocalcification of a large part of the enamel except for a very narrow zone at the enamel surface and a broad zone at the amelodentinal junction.

(Fig. 5B). These findings were borne out by the findings in unerupted teeth from 2 of these cases, though it is unlikely that calcification had been fully completed in either.

In group 5, eight teeth from one case were examined. The localized zones of chipping in the erupted teeth were surrounded by marginal areas of hypocalcification but the most interesting results were obtained from examination of the unerupted teeth. The patient was 16 years of age and it is presumed that the unerupted teeth had completed their calcification. They showed the enamel intact with localized areas of gross hypocalcification corresponding exactly to the deficiencies in the erupted teeth, but at the enamel surface was a very narrow zone of well-calcified enamel, and the hypocalcification did not reach the amelodentinal junction (Fig. 6B). In this case the clinical fault and the hypocalcification both occupied the incisal third of the enamel of the buccal surface of each tooth. In some of the posterior teeth, both erupted and unerupted, a similar zone of hypocalcification was found in a corresponding site in the lingual enamel (Fig. 6C). This latter zone was less hypocalcified than the buccal fault and it seems that such zones may be found in similar positions in other teeth with more careful radiography.

Five groups of amelogenesis imperfecta are therefore apparent, of which one group includes 2 subgroups which seem to be related. The cases in group 1 show hypoplasia with pitting of the enamel, which is hard and normal in texture. There is no staining and no hypocalcification (Fig. 1).

In group 2 there is hypoplasia with wrinkling and grooving of the enamel surface. The enamel is hard but shows, in the available specimens, a zone of marked hypocalcification next to the amelodentinal junction. This zone is parallel to the enamel surface (Fig. 2).

Group 3 shows a marked thinning of the enamel, which is chalky in texture and stained a yellowish-brown. It is probably generally hypocalcified and chips fairly easily. Available specimens show a zone of hypocalcification of varied width which does not involve either the enamel surface or the enamel at the amelodentinal junction (Fig. 3). In one case included in this group no hypocalcification has yet been demonstrated.

Group 4A shows no hypoplasia. The teeth are stained yellow to light brown and the enamel has a slightly chalky texture. Chipping tends to occur only around fillings. The enamel of the available specimens shows hypocalcification throughout almost the entire thickness but zones of well-calcified enamel remain at the amelodentinal junction and at the enamel surface (Fig. 4). The zone at the surface tends to be very well calcified and definitely thicker than in group 4B.

In group 4B the teeth show no evidence of hypoplasia except in one case previously mentioned. The enamel seems to break down very rapidly after eruption and when examined soon after eruption it is cheesy in consistency. All the teeth are heavily stained but on those which have been erupted for some time a thin hard layer remains over the dentine. The teeth showed gross hypocalcification of a large part of the enamel leaving only a very narrow linear zone of well-calcified enamel at the surface, and a broader zone at the amelodentinal junction (Fig. 5). The zone of hypocalcification seemed to be nearer the surface than in group 4A.

In group 5 the teeth show no evidence of hypoplasia. In general the enamel is hard and there is little or no staining or chipping except in localized areas. These areas were found in the middle or incisal third of the buccal surface of each tooth. In the cases examined, the faults varied from staining alone in one case, to gross localized chipping of all erupted teeth in the other two cases. In the unerupted teeth available from the latter type of case, the enamel was grossly hypocalcified for almost the whole thickness of the enamel in the same site as that in which chipping occurred. The hypocalcified zone left a narrow zone of well-calcified enamel next to the amelodentinal junction and a very narrow linear zone of well-calcified enamel at the surface (Fig. 6).

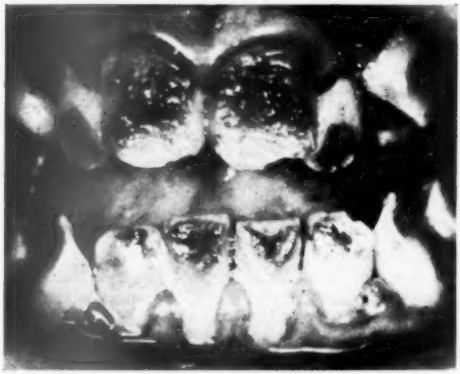

FIG. 6A.—Case from group 5 showing localized areas of chipping and staining in the incisal third of the labial enamel of all teeth.

FIG. 6B.—Radiograph (×5) of an erupted molar from the same case, showing localized zone of hypocalcification in the buccal enamel.

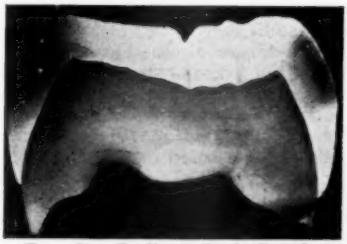

FIG. 6C.—Radiograph (×5) of an unerupted molar from the same case, showing localized zones of hypocalcification in both buccal and lingual enamel.

Hereditary cases occurred in all groups except group 1, and idiopathic cases in groups 1, 4A, 4B, and 5. No evidence of sex linkage has been detected.

There does not appear to be any clearly-defined division of the cases observed into hypoplastic and hypocalcified groups. As described, cases were observed with hypoplasia alone, with hypocalcification alone, and with both hypoplasia and hypocalcification present in the same patient.

The dentine has not yet been fully investigated, but so far no serious disturbance of dentine structure has been noted.

Staining and chipping seem to be closely associated with the degree of hypocalcification and in particular with the proximity of the hypocalcified enamel to the surface. These features were always worst when there was only a very narrow zone of well-calcified enamel at the surface, as in group 4B. Presumably this was easily lost by abrasion exposing the hypocalcified enamel beneath. Where the surface zone was thicker there was less staining and although the enamel tended to be chalky it chipped mainly around fillings. Here, presumably, the surface zone was sufficient to withstand abrasion. In general there appeared to be a marked tendency, in hypocalcified teeth, for zones of well-calcified enamel to be left both at the amelodentinal junction and at the enamel surface. The zones of hypocalcification, except in group 5, always ran roughly parallel to the amelodentinal junction and the enamel surface. They were quite unrelated to the striæ of Retzius except perhaps in one tooth from a case in group 2. The histological examination of the enamel has not yet been completed and it is therefore impossible to discuss prism alignment and organic structures. For this reason no explanation of the hypoplasias can be offered at present.

Diamond and Weinmann (1940) and Weinmann, Svoboda and Woods (1945) described cases which correspond very closely in their clinical description to those described in group 4B. They explain these cases by their theory of maturation of the enamel and use them as a strong support for their theory. In this they describe two stages of calcification. The first, occurring soon after matrix formation, produces calcification up to approximately one-third of the final calcium content. The second, which they call maturation, begins, so they say, at the incisal or cuspal margin and passes downwards through the enamel in a horizontal plane. On this basis they suggest that in their cases of the hypocalcified variety of amelogenesis imperfecta, maturation has failed. If this were so one would expect the whole of the enamel to show an even degree of primary calcification, or perhaps in some cases a horizontal line of junction between mature and immature calcification. In the present series of 21 cases of six different types of amelogenesis imperfecta no such cases have been found. In all cases except group 5, the hypocalcified faults run roughly parallel to the enamel surface and there is a strong tendency in all cases for the superficial and deep enamel to be well calcified. Indeed, in group 2 the enamel appeared to be quite normal in texture on clinical examination and the outer enamel seems to be quite normal in histology and radiography with soft X-rays, in spite of the gross hypocalcification within. There appear to be two zones of mature and immature enamel, but these run parallel to the enamel surface and not horizontally across the tooth. It is therefore clear that the faults observed are not caused by failure of maturation as described by Diamond and Weinmann (1940).

The pattern of the hypocalcified faults described is quite inexplicable on a chronologic basis as, though all the teeth are similarly affected, they develop and calcify at very different ages. No satisfactory explanation can be given at present, but the distribution of the faults in all cases except group 5, strongly suggests that the process of calcification, which is disturbed to produce them, is either a centripetal or centrifugal process, passing between the amelodentinal junction and the enamel surface, from one to the other, or possibly a combination of both. Such possibilities have been suggested by several authors who have investigated calcification in developing teeth. They are even supported by the soft X-rays of Applebaum shown by Diamond and Weinmann (1940) to support their own theory. These show, quite clearly, a well-calcified zone of enamel extending down the amelodentinal junction well in advance of the calcification of the rest of the enamel. They interpret this as an artefact, but recent work by Engfeldt *et al.* (1954) shows it to be a true picture of calcification. It seems reasonable to deduce from these radiographs that the enamel at the amelodentinal junction is fully calcified, or nearly so, well in advance of the rest of the enamel. Calcification may then spread outwards from the amelodentinal junction towards the surface, starting at the incisal margin and working down to the cervical regions as in the diagram (Fig. 7).

All the hypocalcified zones in the cases described in this investigation, except those in group 5, could be explained as faults in such a process, though it is difficult to understand why they seem to occur so regularly in the same anatomical sites. It may be that there is, in fact, a priority for calcification of the enamel at the amelodentinal junction and at the enamel surface, while the rest of the enamel suffers a disturbance, much as the teeth may be well calcified while bones are faulty in systemic disturbances, but this does not fit all cases.

Primary. Secondary.

FIG. 7.—Enamel calcification.

In fact, as there is no evidence of any fault in bones, while calcium and phosphorus metabolism is apparently normal, and as the dentine is probably unaffected, it seems more likely that the fault is local within the tooth germ and is related to the local factors which precipitate calcification rather than to a fault in the supply of the materials. One might perhaps go further and suggest that the fault may be in the preparation of the matrix for the reception of the calcium salts, as in one case from which decalcified sections have been examined the enamel matrix looks very abnormal.

The occurrence of resorption of the enamel in 2 cases from group 3, in teeth before the normal time of eruption and almost before the enamel should have completed calcification, seems to suggest a degeneration of the enamel organ or its successor, allowing mesodermal elements to gain access to the enamel, as suggested by Weinmann, Svoboda and Woods (1945). Such a process may have occurred to a lesser degree in other cases, without being noticed on clinical radiographs.

The cases in group 5, presuming that all show the same local hypocalcification as that seen histologically and radiographically in one case, are extremely difficult to explain and no suggestion can at present be offered.

Summary.—It seems that the cases described show six different types of fault occurring in amelogenesis imperfecta. No satisfactory explanation of the faults can be given, though the zones of hypocalcification are quite inexplicable as faults in the process of maturation described by Diamond and Weinmann (1940). The faults, except those in group 5, would be consistent with a process of secondary calcification occurring in a centrifugal or centripetal manner between the dentine and the enamel surface, or as a combination of both. To explain the faults in group 5 it seems probable that another process, as yet undescribed, must be invoked. The faults seem to be of local origin in the tooth germ and are related to a stage in the process of calcification, or the preparation for it, rather than to any systemic factor.

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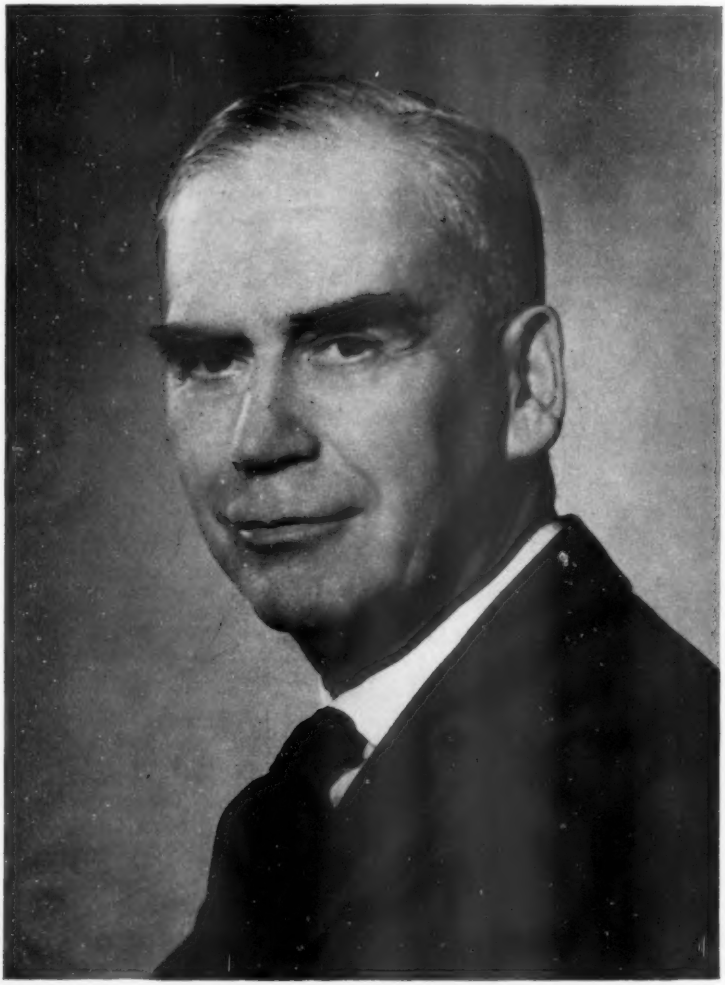
SIR WILLIAM GILLIATT

SIR WILLIAM GILLIATT,

K.C.V.O., M.D., M.S., F.R.C.P., F.R.C.S., F.R.C.O.G.



PRESIDENT

1954 — 1956

AT a meeting of Council, held on October 16, 1956, the death of Sir William Gilliatt was reported in the following way:

Sir Clement Price Thomas (*President*)

It is my sad duty officially to report to this Meeting of Council, the death of Sir William Gilliatt. It was not my privilege to know Sir William intimately, although we met first as long ago as 1940. At this time I was attached to a Chest Unit which was working with King's College Hospital at Horton. One quickly realized the depth of respect and affection in which he was held; it also soon became obvious that beneath a casing of shy reserve, there existed a warm personality only too ready to render service wherever it was required.

Sir William's fatal accident occurred three days before the end of his term as President. My acquaintance with him within the Society was but short and evanescent; in consequence, I have asked Sir Francis Walshe to pay a tribute to all that he did for our Society.

Sir Francis Walshe (*Past President*)

MR. PRESIDENT,

It is in obedience to your wish that I rise to pay a tribute on behalf of the Royal Society of Medicine to its late President, Sir William Gilliatt.

It is only at your bidding that I could presume to speak on this occasion, for there must be Members of Council, who, as old friends, hospital colleagues, or as followers of the branch of medicine that he adorned, are better fitted in every way to pay this tribute.

Indeed, in *The Times* and in the medical press glowing tributes have been paid to him, covering every side of his life and work. My remarks may fitly be confined therefore to Sir William Gilliatt as President of this Society, and perhaps in this role it is true to say that I have been well placed to know and to appreciate what he has done for the Society. It was my lot first to approach him as to his willingness to accept office, and to be met by what was an almost invincible reluctance on his part to do this. This feeling, as I was soon to discover, did not spring from any unwillingness to accept responsibility or the burdens of office at a time of life when most men begin to discard some of their commitments. He might well have shrunk from the office of President at a time in the history of the Society when its future and its financial stability were perhaps more in question than at any time of its existence, and when decisions of grave import impended.

It was, in fact, a genuine modesty that made him hesitate, a feeling that perhaps he could not do justice to the office, and a determination not to be a mere figurehead in a position that might not give him due opportunities for service.

He seemed unaware of certain fine aspects of his character and personality that were an important element in his distinction, and that had engendered for him a widespread respect and admiration.

Having once allowed himself to be persuaded to accept office, he made it his prime business to serve the Society without any reserves, and I think I speak for all the Honorary Officers of the Society when I say that he was completely easy in his relations with us, receptive to suggestions, with immense patience in discussion, willing to change his mind if this seemed right, but standing by his own point of view modestly but firmly when he had made up his mind.

He has been called taciturn. This is not my experience, nor, I feel sure, that of any of us at Officers' meetings, at meetings of Council or of the Finance and General Purposes Committee or upon informal occasions. He may not have worn his heart on his sleeve, but he had a heart and was a most considerate and thoughtful man towards us all, from his colleagues to every member of the Society's staff.

He gave unsparingly of his time and thought, and went to infinite trouble to understand all the issues that determine the successful working, and the future well-being of the Society.

Beneath these virtues, and their sure foundation, were the intellectual and moral integrity, and the unselfishness that mark the complete man.

Sir William Gilliatt served this Society well, and I propose, Mr. President, that a message of appreciation and of sympathy be sent on behalf of the Society to Lady Gilliatt and her family.

This Resolution was then passed whilst all those present stood in silence:

> That the Council of the Royal Society of Medicine wishes to record the deep sense of the loss which the Society has sustained by the death of the late President, Sir William Gilliatt, and to express to his family the Society's sympathy with them in their bereavement.

JOINT MEETING No. 5

Section of Pathology with Section of Epidemiology and Preventive Medicine

Chairman—MAURICE MITMAN, M.D., F.R.C.P., D.P.H.
(President of the Section of Epidemiology)

[*February* 21, 1956]

SYMPOSIUM: CHRONIC BRONCHITIS

Dr. D. D. Reid (Reader in Epidemiology and Vital Statistics, Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine):

General Epidemiology of Chronic Bronchitis

In these introductory remarks, I take as a working definition of the disease—"that condition which is described as 'chronic bronchitis' by general practitioners when they complete certificates of cause of incapacity or death"—for, in the initial stages of an epidemiological study, we are entirely dependent on the broad pictures which such data provide.

Fig. 1 shows that chronic bronchitis, as thus defined, ranks in importance as a cause of death in this country with arteriosclerotic heart disease: among the General Post Office staff, for example, it is the recorded cause of 15% of premature retirements from work on grounds of ill-health (Roberts and Reid, 1954). Like coronary heart disease and cancer of the lung, it is largely a disease of males and accounts, with the other two, for most of the ominous middle-age excess in contemporary male mortality.

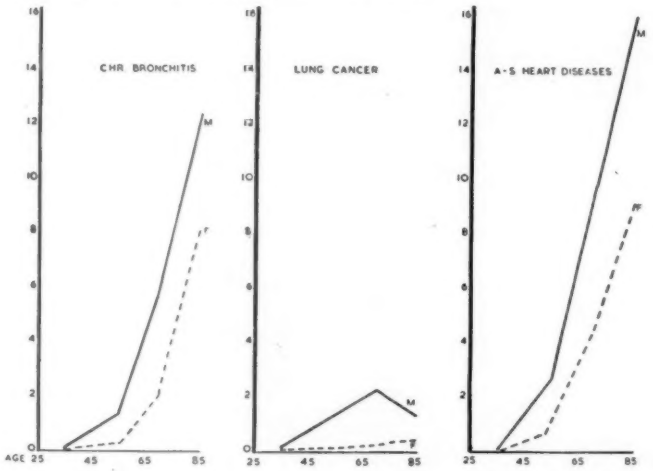


FIG. 1.—England and Wales 1951 death rates/1,000 p.a.

Since it is so markedly a disease of males, and since this symposium has an international flavour, we can start our search for clues about causation by comparing, as in Fig. 2, the crude male death rates ascribed to bronchitis in the countries of North-West Europe. There is a remarkable gradient from the very low rates of Norway and Denmark, the slightly higher rates of Sweden, France and Switzerland, and the greater mortality in Western Germany, the Netherlands and Belgium, to the peak rates of the British Isles in general and of England and Wales in particular. In terms of relative frequency at least, chronic bronchitis is a modern analogue of the "English sweats" of the sixteenth century, and it is a happy coincidence that one of the best descriptions of that other epidemic respiratory

catarrh came in 1580 from Professor Mulder's predecessor in the faculty of medicine at Leiden, Peter Foreest (Withington, 1894).

Concentrating on England and Wales, we see in Fig. 3 that, although there is a general increase in the death rates as we pass from South-East to North-West, the main concentrations

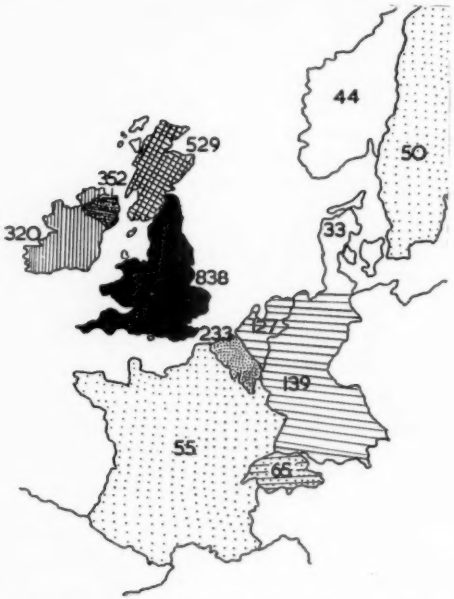


FIG. 2.—Bronchitis mortality in N.W. Europe. Crude male death rates/million p.a., 1952.

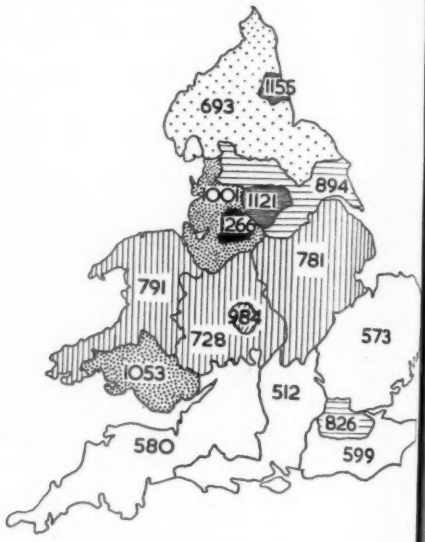


FIG. 3.—Bronchitis mortality in England and W
Rates per million, 1950.

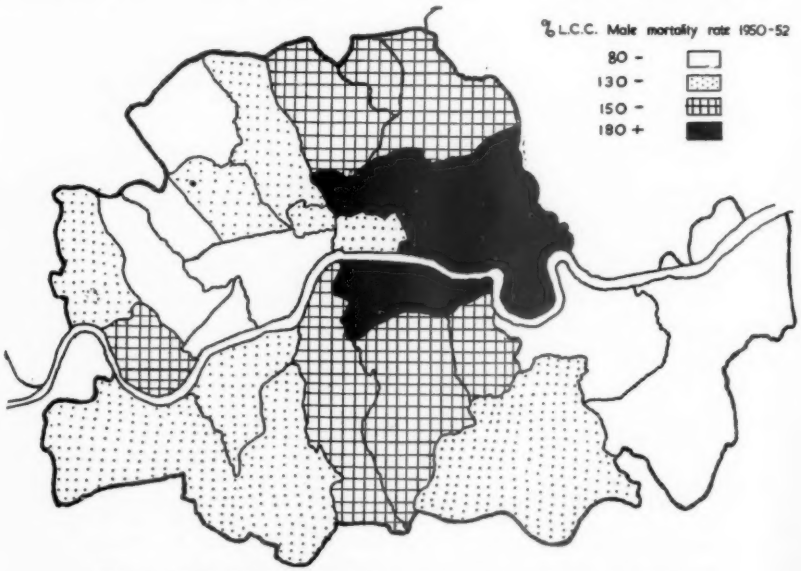


FIG. 4.—Bronchitis mortality in London. Male mortality ratio 1950-52.

of high bronchitis mortality are in the great industrial conurbations which stand out, even in the North-West, from the surrounding districts.

Even within an urban area like the County of London, where climatic conditions of temperature and humidity are reasonably uniform, there is an area of excessive bronchitic mortality in the central and north-eastern parts of the county (Fig. 4).

Interpretation of these spatial contrasts is extremely difficult. The black areas certainly are the districts most affected by industrial and domestic smoke pollution. The smog of 1952, for example, was most intense there. But equally, they house the semi-skilled artisans and labourers who are exposed by their jobs to physical exhaustion, to the weather and to industrial dust and fumes. With their wives, these men share the risks of multiple infections in congested areas and overcrowded homes. These social and environmental factors, together with inadequate diet and medical care, have all been indicted as causes of the steep social-class gradient in both male and female mortality rates which is so striking a feature of chronic bronchitis.

In a disease where many causative factors are implicated, the problem is to try to isolate and measure the effects of even a few of them. Some of the inherent difficulties can be resolved, however, by what has been termed the "artichoke" principle in scientific investigation. The general idea of this approach in epidemiological enquiry is to measure the isolated effect of one factor at a time, by comparing the incidence of disease in two population groups where all relevant factors except that one have been kept constant. The same process is continued by dividing and comparing the population in different ways until, factor by factor, the problem has been dissected.

The staff of the General Post Office forms a particularly suitable population for such a method. It includes men and women doing standardized jobs at similar rates of pay spread fairly evenly over the country, uniformly selected and under the overall medical supervision of the Treasury Medical Service.

Thus we can isolate the effect of sex differences by comparing the incidence of bronchitis in men and women of the same age, doing similar indoor office jobs, in the same district at the same time. The experience of male and female London office workers set out in Fig. 5 shows that the male excess in later life, seen in sickness as in death, cannot be entirely explained by differences in climatic exposure, range of infective contacts or the physical demands of men's and women's work. Whether it is simply another aspect of male biological inferiority or, as Oswald and Medvei (1955) have recently suggested, the result of habits like heavy smoking, remains to be seen.

Similarly, we can concentrate on the effect of job differences on bronchitis morbidity by comparing, as in Fig. 6, attack rates in men doing physically more arduous outdoor work as

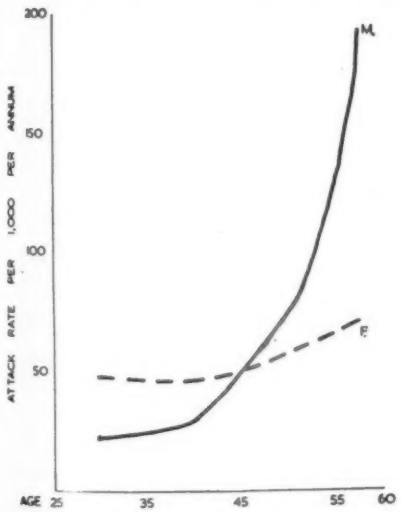


FIG. 5.—Bronchitis in London clerical workers.

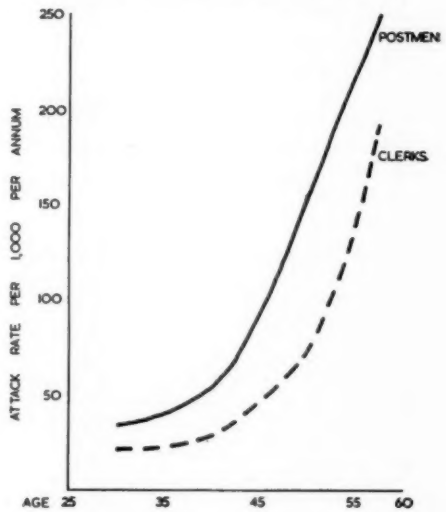


FIG. 6.—Bronchitis in male London postal workers.

postmen with those in men of the same age in the same district at the same time but working as clerks. In so far as absence from work is a reasonable measure of incidence, bronchitis is much more frequent in the postmen who spend much of their lives outdoors in London. Postmen in Greater London share the same climate, the same job and the similar social circumstances which go with standard rates of pay. Since the doctors of the Treasury Medical Service try to ensure reasonably consistent clinical standards of invaliding from the postal service, we can use the bronchitis invaliding rate as an index of clinical response to the street environment in different parts of London. Thus in Fig. 7 we divide the whole area, through the City centre, into four quadrants and compare the annual bronchitis invaliding rates for the central area and each of these quadrants. If we then assume, as Stocks did in his study of cancer of the lung (Stocks, 1952), that the prevailing west-south-west wind will cause a build-up in smoke pollution over the centre and north-east of the area, the gradient in rates from South-West (2·6) to North-East (4·5), is, to say the least, suggestive.

Finally, lest we become hypnotized by the idea that smoke pollution is the all-important factor, we can compare in Fig. 8 the trends in national male mortality rates from chronic bronchitis with contemporary trends in sickness-absence rates in Post Office workers spread over the whole country. These absences are largely due to virus infections of the respiratory tract and the close time-correlation seen here re-emphasises the role of epidemic infections, such as the influenza outbreak of 1951, in causing death in the chronic bronchitic. One might also note the apparent failure of antibiotic therapy to achieve any major consistent drop in bronchitis death rates in recent years.

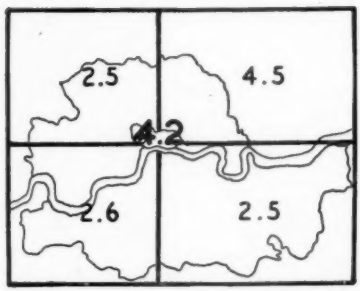


FIG. 7.—Bronchitis invaliding rates in London postmen (per 1,000 p.a.).

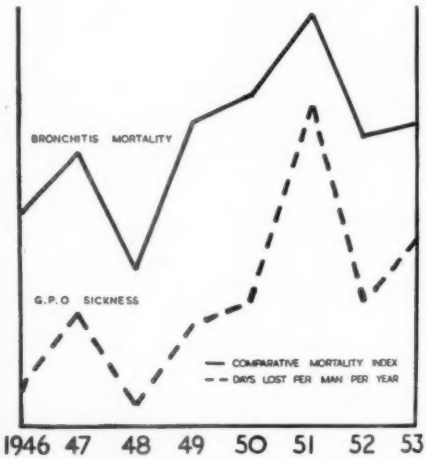


FIG. 8.—Trends in bronchitis mortality and total sickness absence rates.

What are these scraps of epidemiological evidence worth? One might suggest that chronic bronchitis is a disease of the industrial countries of North-West Europe in general and of England in particular. Although death from chronic bronchitis is most frequent in the poorer working-class districts of the industrial cities, smoke pollution seems to have an effect on sickness which is independent of differences in nature of work and standard of living. Again, the undue susceptibility of the middle-aged male cannot be entirely explained by differences between the contacts, physical demands or climatic exposures of men's and women's work. Finally, whatever the predisposing causes, whether of environment, physique or personal habit, the common respiratory infections appear to be major precipitants of serious disability and death in a disease whose importance is matched only by our ignorance of it.

I am indebted to Dr. W. Chiesman of the Treasury Medical Service for his help and for permission to publish some of these data.

SUMMARY

A survey is made of epidemiological evidence on the numerical importance of chronic bronchitis as a cause of death in various parts of North-West Europe and as a cause of sickness in the staff of the General Post Office in London. The unusually high frequency of death from chronic bronchitis among the males of the industrial areas of England is remarked upon, and some evidence for the ætiological importance of smoke pollution and of infection is reviewed.

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Dr. Lynne Reid (Institute of Diseases of the Chest, London):

Pathology of Chronic Bronchitis

The morbid anatomy of chronic bronchitis cannot yet be presented as a complete picture, which relates its beginnings and progression to the causes which may operate, for these causal factors are still largely unknown. Further, the disease has no specific or diagnostic lesion: its most characteristic feature seems rather to be the pattern of involvement of the lung. Even if in the early stages of chronic bronchitis the changes are confined to the bronchi, in the later stages pathological changes are also present in the bronchioles and respiratory part of the lung.

The earliest and most constant clinical feature in chronic bronchitis is the production of sputum, which reflects hypersecretion of bronchial mucus. Mucus is normally secreted from goblet cells in the bronchial epithelium and from mucous glands in the walls of the bronchi. The glands have the same distribution as the cartilage, and, like the plates of cartilage, are fewer in number in the more peripheral bronchi. The number of goblet cells in the epithelium also decreases progressively towards the periphery, so that there is only an occasional one in the wall of a bronchiole. Except in the bronchi, therefore, there are relatively few mucus-producing cells in the normal lung.

In chronic bronchitis the increased production of mucus is reflected by an increase in the number of cells which contain mucus. The mucus may be present only in the form of mucinogen granules at the base of the cell, or the cells may be distended with mucus or in process of discharging it. There is also an increase in the number of goblet cells in the ducts of the mucous glands and the amount of mucinous material in the cells of the acini is greater. The number of goblet cells in the bronchioles is also increased, although the changes here may vary in different parts of the lung. Usually, however, in operation or autopsy specimens from patients in whom chronic bronchitis has been present for some years, changes are also present in the peripheral part of the lung, within the secondary lobules. The changes here are varied. There may be acute purulent bronchiolitis, or there may be scarring which suggests previous damage to bronchioles. The bronchioles may be dilated or obliterated, or the combination of dilatation and obliteration may convert them into cysts. The alveoli also show a variety of changes: pneumonic consolidation, collapse, abscess formation, emphysema, œdema, fibrosis. These changes in the bronchioles and alveoli, although listed separately, are related. The changes include some which are acute and others which are chronic, and some which could resolve and others which have already produced irreversible damage.

These changes may be illustrated by the findings in serial histological sections cut through a block of tissue which was taken at autopsy from a part of a lung which macroscopically appeared to be relatively normal. The patient was a man of 64 who had a history of chronic bronchitis over many years. He had noticed shortness of breath for six years before his death, and he had been in hospital several times because of exacerbation of his symptoms. Three secondary lobules were traced through the serial sections. The first lobule showed bronchiolectasis—the bronchiole expanded into a cystic area which was surrounded by scarred, collapsed lung, in which one of the side bronchioles ended blindly. In the second lobule there was a small focus of pneumonia around one of the bronchioles, and adjacent to another bronchiole there was a microscopic abscess cavity which had ulcerated the bronchiolar wall at one point. The third lobule, although of approximately the same diameter as the other two, was in fact the scarred remnant of a considerably larger volume of lung. An elastic-tissue and van Gieson stain showed the remains of collapsed lung with the dilated branches of the bronchial tree in the centre. The regular arrangement of the muscle fibres showed that ulceration had played little part and that dilatation was the main reason for the increase in diameter.

The third of these lobules had been palpable in the lung as a firm nodule about the size of a cherry stone. In some patients with chronic bronchitis many such nodules are palpable: to gain some idea of their frequency, and of the pathological changes which they represent,

FIG. 1.

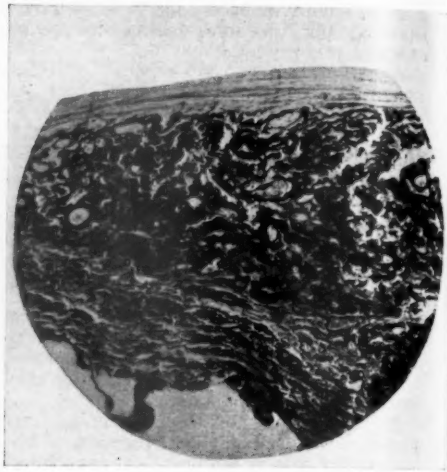

FIG. 2.

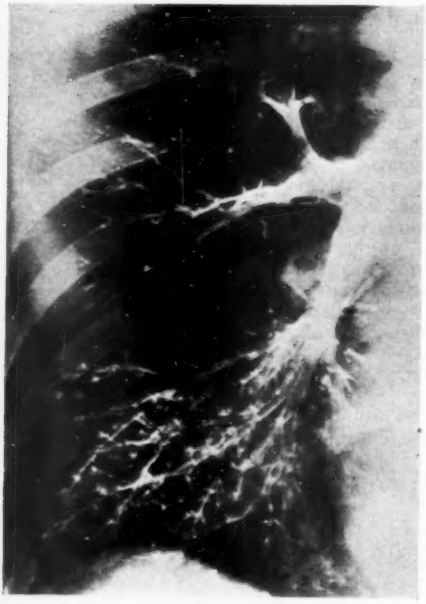

FIG. 3.

FIG. 1.—Nodule of condensed lung showing homogeneous appearance when stained with hæmatoxylin and eosin. It lies deep in the lung. × 12·5.

FIG. 2.—Subpleural nodule stained to show elastic fibres (black), and illustrating the condensed pattern of the lung. (Verhoeff and van Gieson stain.) × 20.

FIG. 3.—Right bronchogram showing pools of radio-opaque material, several millimetres in diameter, in the peripheral part of the lung of a patient with chronic bronchitis.

thirty-two lobes from twelve patients with chronic bronchitis were studied. It was found that the diameter of the nodules ranges from several millimetres to one and a half centimetres. Deep in the lung they usually feel spherical; but in the subpleural region they are often flatter, and may be so shallow that they are dismissed as pleural thickening. These lesions look

more impressive in thin stained sections than they do in the gross specimen: in the latter, if they are surrounded by normal-looking lung they are not obvious, while if there is emphysema around them they are usually overlooked because the emphysema is more impressive. The nodules are not rare, but they are irregularly distributed: for example, in one patient eighteen nodules were counted in one lobe and five in another, while in three lobes there were none at all. Histologically these nodules appear homogeneous when stained with hæmatoxylin and eosin (Fig. 1). An elastic tissue and van Gieson stain is necessary to distinguish pneumonia from collapse (Fig. 2). Of the nodules studied histologically about one-half showed predominantly pneumonia, rather more than one-quarter showed predominantly collapse, and in the remainder fibrosis was so dense that the nature of the change could only be recognized with difficulty. In two-thirds of the total fibrosis was considerable.

These nodules, then, represent localized changes of different ages in the peripheral part of the lung. Although much of the acute change doubtless resolves, the dense fibrosis in some nodules suggests that scarring is not an infrequent result. The volume of normal lung which these nodules represent is considerably greater than their own final volume.

Bronchography in patients with chronic bronchitis readily shows the results of these pathological changes. There are two main bronchographic changes in the peripheral parts of their lungs. The first is the absence of peripheral filling. Deficient peripheral filling may result from technical inadequacy, or from sputum in the lumen of the bronchial tree, in which case the ending is usually squared. Often, however, and particularly when the end of a bronchiole is rounded, the failure to fill results from the obliteration of the bronchiole in a scar. The second feature is the presence of peripheral pools of contrast medium several millimetres in diameter (Fig. 3). From examination of the lung these pools can be shown to represent bronchiolectasis.

I have presented the pathological changes in chronic bronchitis in two parts; this has the convenience of corresponding approximately to an anatomical division. The first part illustrates the disturbance of mucus secretion and is concerned mainly with the bronchi, while the second represents the changes in the respiratory part of the lung, that is, in the bronchioles and alveoli. This division has a further use; in the present state of our knowledge of chronic bronchitis, it is useful, although doubtless an oversimplification, to think of these two aspects as posing separate questions. The disturbance of mucus secretion presents the problem of the fundamental cause or causes of chronic bronchitis; on the other hand, the increasing involvement of the peripheral part of the lung presents us with the problem of the clinical progression of the condition. The various lesions that have been demonstrated and the different factors that influence them, such as infection, climatic conditions and occupational environment, should therefore be assessed separately in relation to the part which they play in these different phases of the disease.

Professor Dr. J. Mulder (Clinic for Internal Medicine, University Hospital, Leiden, Holland):

Bacteriology of Bronchitis

I. Chronic Bronchitis

Chronic bronchitis is a clinical diagnosis which relates to a number of different inflammatory conditions of the bronchi. Excluding tuberculous bronchitis and other rare forms of bronchitis, e.g. bronchomycosis, one can distinguish four groups of chronic bronchitis.

(A) "Allergic" bronchitis (eosinophilic, asthmatic, or bronchospastic bronchitis; Laennec's *catarrhe sec*). Patients with "allergic" bronchitis present the following manifestations: (1) Chronic cough. (2) Expectoration of viscid, "mucoid" sputum, which is usually scanty and which microscopically shows predominance of eosinophil leucocytes and macrophages; these sputa do not show a pathogenic bacterial flora. (3) Sometimes, on bronchographic examination, a spastic bronchial tree can be shown to exist, without bronchiectasis or bronchial deformation. (4) Some of the patients never suffer from attacks of bronchospasm (asthma); others have a number of these attacks, and some develop chronic bronchospasm which often leads to severe emphysema and gives rise, after a varying number of years, to manifestations of cor pulmonale.

(B) The second group, which is not common, comprises patients suffering from chronic mucopurulent bronchitis, without evidence of allergic bronchitis. The manifestations are the following: (1) Chronic productive cough. (2) The production of mucopurulent sputum which always contains a pathogenic aerobic flora. (3) Absence of eosinophils in the sputum and of bronchospasm. (4) Absence of general emphysema. (5) Rapid development of bronchiectasis and bronchial deformation. (6) Clubbing of the fingers. (7) Development of amyloidosis in long-standing cases.

(C) The third group, which includes the greatest number of patients suffering from chronic bronchitis, is a combination of groups A and B. In our material about 80% of patients suffering from bronchiectasis belong to this group. In many cases the symptoms of asthmatic bronchitis prevail, in other cases those of mucopurulent bronchitis. Sometimes the underlying asthmatic condition becomes manifest only after a period of treatment with antibiotics: in these cases the patients continue to expectorate mucoid sputum containing eosinophil leucocytes. During and after antibacterial treatment some patients develop a very severe bronchospasm, which may be fatal.

(D) The fourth group is made up of cases of chronic fetid mucopurulent bronchitis and is not strictly a separate one. The sputum is foul and bacteriologically shows a multiple, partly anaerobic flora. Some cases are associated with ozæna (tracheal and bronchial ozæna) and do not develop bronchiectasis. Most cases belong to the group of mucopurulent bronchitis and are nearly always associated with bronchiectasis. There is no correlation between the appearance of fetid sputum and the diameter of the diseased bronchi. Fetid sputum most probably only appears in cases in which the ciliated bronchial epithelium undergoes metaplasia, with the development of squamous epithelium (Mulder and Hers, 1955).

A screening method for the investigation of eosinophilia in the sputum.—For many years we have used the following technique for demonstrating eosinophil leucocytes: fragments of sputum are washed in buffered saline and stained in a solution of 0·05 gram of eosin and 1·0 ml. of 40% formalin in 100 ml. of distilled water (Zollikofer's solution). The sputum is gently compressed under a cover glass and studied at low magnification. The eosinophilic granules are stained dark red. The neutrophil cells are uncoloured but clearly visible.

The bacteriological flora in mucopurulent bronchitis. Technique of the bacteriological examination of the sputum.—We believe that a preliminary Gram stain of the sputum is necessary in order to obtain correct results. In the first place the Gram stain serves as a control to ensure that the sputum has been properly washed, for pharyngeal or oral mucus can be identified by the presence of squamous epithelial cells, which usually contain micro-organisms. The presence of oral and pharyngeal flora is a further indication of inadequate washing of the sputum. The second reason for the preparation of a Gram stain is the fact that the stained preparation may reveal bacteria which may not grow well on artificial media, e.g. *Hæmophilus influenzæ*, Klebsiella, and anaerobic organisms. The investigation is carried out on sputum which has been expectorated into a Petri dish. The specimen is examined against a black background. A very small piece is isolated with a loop and washed successively in three Petri dishes containing buffered saline. The piece is then dried as much as possible by pressing out the saline, as smears of wet sputum do not give reliable microscopic pictures. Smears are made on glass slides: duplicate preparations are stained by Gram's method and with methylene blue. Sometimes, especially in chronic infections with *H. influenzæ*, micro-organisms can be seen only within the leucocytes. In general, a tentative identification of the pathogenic genera present in the sputum can be made with reasonable certainty from the Gram preparation.

Culture media.—We use for each culture blood-agar and Levinthal-agar (plates and tubes) and also a tube containing blood-serum broth for the selective growth of pneumococci (this medium is as reliable as mouse inoculation).

Fetid sputum should be cultivated anaerobically since *H. influenzæ* which may be present in these sputa grows only anaerobically in the primary culture.

The importance of bacteriological examination of sputum from cases of bacterial bronchitis is that an adequate antibiotic can be chosen for treatment. Antibiotic treatment should be given (1) before bronchographic examination is done, in order to rid the bronchial tree of as much mucopurulent exudate as possible, so that the exudate will not prevent proper filling of the bronchi by the contrast medium; (2) before and after surgical treatment of bronchiectatic lobes or segments, and (3) when the condition is too extensive for surgical treatment.

Incidence of pathogenic genera in cases of mucopurulent bronchitis (*Tables I and II*). H. influenzæ *group.*—From Tables I and II it can be seen that the *H. influenzæ* group is the most important group of organisms pathogenic to the mucosa of the respiratory tract (Mulder *et al.*, 1952; May, 1954). 95% of all strains isolated from adults are unencapsulated and the remaining 5% are encapsulated. Most encapsulated strains belong to the Pittman subgroups B and F; other subgroups are occasionally present. The underlying mechanism of this distribution is unknown but merits further research. The finding of a subgroup B infection in the bronchi is also important from an epidemiological point of view because it shows that adults may carry these strains and may in this way form a source for cases of septicæmia, meningitis and phlegmonous laryngitis in children below the age of 10. Unencapsulated *H. influenzæ* is definitely pathogenic in the airways: its elimination by antibiotics causes the disappearance of the toxic symptoms of inflammation and halts the production of mucopurulent sputum (Mulder *et al.*, 1952). In chronic cases, recurrences or relapses of inflammation are very common.

TABLE I*.—BACTERIAL FINDINGS IN ACUTE AND CHRONIC MUCOPURULENT BRONCHITIS (1946–1950)

Clinical diagnosis	Genus																
	H. influenzæ	Pneumococci**	Neisseria	Klebsiella	*E. coli*	*Staph. aureus*	*Strept. hæmolyticus*	Proteus	*Ps. pyocyanea*	Anaerobic	*H. influenzæ* + Pneum.**	*H. influenzæ* + Neiss.	*H. influenzæ* + Klebs.	*H. influenzæ* + alpha hæmol. strept.	*H. influenzæ* + *Staph. aureus*	*H. influenzæ* + *E. coli*
Acute mucopurulent bronchitis	19	1	3								3				1	
Acute mucopurulent bronchiolitis	2															
Asthmatic bronchitis with acute or subacute bacterial bronchitis ..	23	12	7		2	4	1				8	2		2	2	
Chronic mucopurulent bronchitis including coexistent asthmatic bronchitis	99	10	5	5	4	6		2	1	6	41	10	3	4	3	5

**After* Van der Plas. (1951).

**The serological types of pneumococci are: 3, 4, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16 ,17, 18, 19, 21, 22, 23, 29, 33, 34, 35 and 41.

TABLE II.—INCIDENCE OF *H. influenzæ* IN CASES OF ACUTE AND CHRONIC MUCOPURULENT BRONCHITIS (1928–1950)

Diagnosis	Cases	*H. influenzæ* %	*H. influenzæ* in practically pure culture %
Acute mucopurulent tracheobronchitis (bronchiolitis) ..	315	83	48
Chronic mucopurulent bronchitis including coexistent asthmatic bronchitis	363	84	50

The pneumococcus group stands next to the *H. influenzæ* group in importance. Chronic mucopurulent bronchitis associated with a pure pneumococcal infection is rare: in most cases *H. influenzæ* is found along with pneumococci. Pure pneumococcal infection is commoner in acute bronchitis. Type III and the higher types of Cooper prevail. We know of one case of chronic asthmatic bronchitis infected with pneumococcus type I without co-existent lobar pneumonia.

The Neisseria group.—In chronic bacterial mucopurulent bronchitis this group is rarely found in pure culture. In acute bronchitis, on the other hand, it may be found as the only causative organism. It never causes bronchiolitis or bronchopneumonia. We find a few cases yearly of acute bronchitis associated with the presence of meningococci.

The Klebsiella group.—We found this group exclusively in cases of chronic mucopurulent bronchitis. We do not know of the occurrence of acute bronchitis caused by this group.

The Streptococcus salivarius *group.*—We found this group in 1·3% of our cases of chronic mucopurulent bronchitis, along with *H. influenzæ*. We have never met with cases of acute bronchitis caused by this group. The high incidence mentioned in textbooks is undoubtedly caused by the faulty bacteriological technique of using unwashed sputum for cultivation.

The groups of pyogenic cocci (*Staphylococcus aureus* and β-hæmolytic streptococcus) are,

in cases of acute bronchitis, nearly always associated with co-existent virus infections (notably influenza and measles), which have a cytotoxic action on the ciliated epithelium. Histological studies show fibrinous necrotising inflammation.

Escherichia coli.—This organism is absent in acute and rare in chronic mucopurulent bronchitis. However, it appears frequently after treatment with penicillin. The pathogenicity of this group in the airways seems to be low. Very often sputa containing *E. coli* do not show a heavy leucocytic exudate.

II. Acute Bronchitis

Acute bacterial bronchitis is difficult to analyse scientifically because many cases are associated with virus infections of the respiratory tract. The explanation of this association is most probably that the respiratory viruses have a cytotoxic effect on the ciliated epithelial cells of the respiratory mucosa and in this way diminish resistance to bacterial infection (Hers, 1955). In the laboratory the viruses of the influenza group (A, B and C) can easily be handled. The same holds true for the new A.P.C.—or A.R.D.—viruses. Measles and coryza are more or less readily recognizable clinically, as is the primary atypical pneumonia associated with cold-hæmagglutination.

Secondary bacterial invaders are well known in influenza and measles, much less so in coryza and still less in the diseases caused by viruses of the A.P.C. group. The existence of primary acute bacterial infections of the bronchial mucosa is doubtful, though there are indications that the groups of *H. influenzæ*, pneumococci and Neisseriæ may be primarily pathogenic (Hers and Mulder, 1953). It is certain that patients with pre-existing allergic (asthmatic) bronchitis are more susceptible than others to acute bacterial bronchitis. Primary bacterial bronchitis may develop in cases of typhoid fever, myocardial infarction and other conditions, and also as a terminal illness.

For the treatment of moderate to severe bacterial bronchitis antibiotics should be used, the choice of antibiotic depending upon the results of bacteriological examination of the sputum. In this way the process can be stopped immediately. In children the bacterial ætiology of a bronchial or bronchopneumonic process sometimes can be ascertained by examination of the purulent nasal discharge which may be associated with the bronchial process. The same holds true for cases of acute sinusitis and otitis.

Acute mucopurulent bronchiolitis (Laennec's *catarrhe suffoquant*). This disease, according to our experience, is always caused by *H. influenzæ* infection. Pneumonic consolidations of any extent are lacking in these cases (*H. influenzæ* pneumonia of the American textbooks does not exist, or is exceedingly rare). The disease is sometimes very severe and may be fatal. Adequate antibiotic treatment may be life-saving.

Transition from acute to recurring and chronic mucopurulent bronchitis.—The mechanism by which an acute bronchitis becomes chronic is still unknown. Working hypotheses are: (1) The acute bacterial bronchitis may be associated with acute sinusitis. The latter may become chronic, causing recurring bronchitis by aspiration of pathogens (about 40% of all cases of chronic mucopurulent sinusitis are associated with *H. influenzæ* infection); (2) acute bacterial bronchitis may cause persistent anatomical damage to the bronchial mucosa, e.g. multiple stenosis (Hers, 1956), which may initiate relapses or recurrences of bacterial bronchitis originating from chronic bacterial foci in the bronchi or by aerogenic reinfection; (3) acute bacterial bronchitis in predisposed individuals may initiate allergic bronchitis, which, in turn, predisposes to recurring bacterial infections.

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Professor C. H. Stuart-Harris (University Department of Medicine, Sheffield):

Field Studies in Relation to Chronic Bronchitis

Study of the causation of a long-continued process such as chronic bronchitis presents peculiar difficulties. The end of the road is a very long way away in terms of years from the beginning of the journey and mortality itself is not necessarily bound to reveal the important circumstances which played upon the patient's respiratory tract at the initiation of his disorder. Perhaps it is this very feeling of insecurity at the many deductions made so far as

a result of a study of mortality which is responsible for a revived interest in morbidity. But, in the case of all chronic disorders, morbidity studies of an epidemiological character cannot be begun unless the diagnosis of the condition is certain. Granted a physical sign, then one can begin to make progress.

Probably there would be a considerable measure of agreement amongst a group of clinicians if they were confronted with a series of patients with advanced chronic bronchitis and emphysema. But one could prophesy an equal measure of disagreement if patients in all stages of the process were assembled and diluted by the presence of an equal number of perfectly healthy persons. The truth is that whereas it is reasonable to ask a clinician to confirm a diagnosis of chronic bronchitis, it is much more difficult to say that a person does not have this condition. Two circumstances appear to be responsible for this difficulty in definition. First of all, in chronic bronchitis, symptoms are much more in evidence than physical signs, and, secondly, chronic bronchitis is particularly common after middle life, and there is a tendency for an alteration of the pattern of acute respiratory infection as one ages, so that colds have a greater tendency to lead to complications. Moreover, dyspnœa is an inevitable accompaniment of the decreasing respiratory function which sets in after 40 and is accentuated by other factors, such as obesity or a more sedentary existence.

The proposition therefore that one should begin to tackle the epidemiology of bronchitis by defining the prevalence of bronchitis in different persons living under different social and environmental circumstances is far from easy. A pilot study which was made in 1951 at an engineering and chemical industrial firm near Sheffield (Stuart-Harris, 1954) served as a clear illustration of the problem. Using symptoms alone, it was possible to correlate age with the prevalence of a history of cough and expectoration which was either persistent or only experienced at intervals, for instance during colds. The addition of dyspnœa of a defined degree to the presence of a persistent daily cough and sputum gave a rather sharper picture similarly correlated with age. The same population surveyed by the combination of physical examination, X-rays and function tests could be subdivided into 3 groups—the healthy, those with organic disease and those with indeterminate findings. The clinical diagnosis in the organically abnormal men showed a complicated mixture of heart and chest disease, with the presence of more than one condition in a significant number. It seemed that the clinical diagnosis of chronic bronchitis was a rather artificial separation of those with persistent cough and sputum, and a history of annual winter attacks, termed bronchitis after exclusion of other conditions of the chest. It follows that one can only obtain a really reliable idea of the prevalence of what the clinician terms chronic bronchitis in a community by the fullest of clinical examinations, to which must be added a chest X-ray and some form of pulmonary function test.

This pilot study led us to a second purely symptomatic study of several thousand workers at the same industrial plant in an endeavour to get away from pure clinical diagnosis. The aim was to subdivide the population into the simplest of symptomatic groups and to attempt to correlate the findings with a history of past illnesses, with occupational factors and with personal factors such as smoking. This second study was carried out by the questionnaire method and the answers to questions concerning respiratory symptoms enabled us to distinguish five categories of persons.

These were: A. those with no history of cough or sputum;
B. those with a dry cough but no sputum;
C. those with cough and sputum experienced only intermittently, such as during colds;
E. those with persistent daily cough and sputum, but no undue breathlessness;
G. those with persistent daily cough and sputum, with the addition of dyspnœa on exertion to a defined degree.

Categories A and B diminished in proportion with age, C remained at approximately the same level in each decade, and categories E and G increased in proportion with increasing age, particularly over the age of 40. Correlation of these symptomatic categories with past illnesses revealed the fact that almost all of those who suffered annually from attacks of bronchitis belonged to category G. Pneumonia in adult life and pleurisy also showed a higher incidence in category G, whereas childhood pneumonia, whooping cough, and nasal symptoms suggestive of sinusitis were not significantly correlated with any category.

It is not my purpose to detail the other results of this survey, which has revealed quite clearly, to my mind, the possibility of obtaining excellent descriptive details of a population by a very simple method. I would however like to refer briefly to the results of a similar study carried out by Dr. Marjorie Clifton, who effected much of the earlier study and who has surveyed a rural population in the North of England. Subdivision of the men over 30 in

Dr. W. N. Pickles' practice in Wensleydale gave results which contrasted with those obtained in Sheffield. The category of persistent cough and sputum without dyspnœa was less clearly correlated with age in this group. There were many fewer men with the three symptoms of persistent cough, sputum and dyspnœa in Wensleydale, but the percentage increased sharply in those over the age of 60. This rural study brought out a new occupational syndrome—new, that is, to those of us who work in towns. Working with hay, particularly at certain seasons of the year, evokes cough, sneezing and dyspnœa in some farmers, and this perhaps is a hazard due to atmospheric pollution not normally visualized by those of us who are obsessed by smoke.

Comparison of the Wensleydale and Sheffield surveys clearly shows the difficulty which exists in establishing a difference in the patterns of symptoms in different populations and then in attempting to relate these to particular circumstances, such as environment or occupation. No two populations are the same even in age and sex structure, and when one attempts to allow for the differences imposed by personal habits, occupation and all that comes under the heading of social conditions, it is practically impossible to evaluate the influence of one specific circumstance such as, for instance, the question of atmospheric pollution.

The working-party of the Medical Research Council's Sub-Committee on Chronic Bronchitis has held many meetings during the past eighteen months in order to seek to guide a programme of research. So little was known about field conditions at first that the results of various field studies now in progress were awaited. We were at first confronted with the difficulties in definition, and we have not been able to arrive at a definition which will obviate the necessity for full clinical examination, including the use of radiography. More recently we have examined the problem of establishing the significance of a reduction in atmospheric pollution, such as may be effected by the efforts of local authorities in the light of the Beaver Report and the Clean Air Bill. It will be very costly in terms of medical man-power to establish prevalence data in different areas where atmospheric pollution already exists to a different extent. Moreover, this information can only be related to past exposure to pollution, and several surveys in the same towns would have to be made if the effect of changes in pollution in the future were to be determined.

An alternative suggestion is that, by means either of surveys or through medical practitioners, panels of chronic bronchitic persons would be established in a number of different towns with different pollution levels. Such individuals would record their experience in terms of health and particularly of attacks of bronchitis. Simultaneously, records of the atmosphere would be kept in order to establish the effect of such measures as might be taken in cleaning up the smoke content of the air. It is not, of course, generally realized that records of pollution as kept at present are totally inadequate for such a detailed experiment as that now visualized. There are great differences over short distances in the actual intensity of pollution, and a large number of sampling stations would have to be set up. Moreover, in large towns or conurbations, a gradual spread of smoke-cleared areas would not produce a sharp enough change in pollution for any short-term study of the clinical effects. Smaller towns, say of 50,000 to 200,000 persons, and ones in which a vigorous attempt at a reduction of pollution could be applied, would be much more suitable.

In these areas where pollution was being reduced, it is probable that other indices such as the vital statistics, sickness absences from industry and even school absences might show a difference and must therefore also be studied. Nor is there any reason for exclusion of the elaborate clinical survey of the type referred to as a prevalence survey. This might also be effected in a few likely areas.

Other Causative Factors

Atmospheric pollution, however, is only one of the probable causative factors of chronic bronchitis. The striking correlation between bronchitis mortality and social class indicates a distinction between the incidence in Classes I and V which must be a reflection of much more than pollution. In any future programme of research there is much to be done in the elucidation of personal factors as well as of environmental ones. There is the question of heredity, of childhood infections and of habits such as smoking. There is the influence of occupation. The latter is a particularly difficult subject to investigate because of the way in which factors are linked. Thus heavy work is often dusty or dirty and it is difficult to select jobs which are heavy and not subject to any atmospheric conditions. Then again, personal factors may be linked with environmental ones—such as, for instance, heavy smoking and occupation. There seems no other way to pursue the matter than to obtain data from as many subjects in as many walks of life as possible. Climate also requires attention and it may well prove desirable to pursue parallel studies in this and other countries. Finally,

I do not feel that we can afford to neglect the detailed study of relatively few persons at different phases of the natural history of bronchitis. The so-called acute exacerbation is still somewhat mysterious. Undoubtedly many attacks are precipitated by infection but I personally favour the view that a deeper knowledge of the various respiratory viruses is required before we shall be able to understand the relative importance of bacteria such as *Hæmophilus influenzæ* in regard to acute episodes. I am still extremely dubious of the significance of the eosinophil cells in the sputum in chronic bronchitis, but, no doubt, studies such as those of Professor Mulder and his associates will, in due course, provide the answer.

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Dr. Horace Joules (Central Middlesex Hospital, London):

The extent of the problem can be measured only partially by statistics, but in 1951 bronchitis was responsible for the certified loss of 26·6 million days among the insured population, while nearly 37,000 people died of the condition (Table I). The introduction

TABLE I.—DAYS OF INCAPACITY FROM BRONCHITIS IN ENGLAND AND WALES, TOGETHER WITH TOTAL DEATHS FROM THIS CONDITION 1951

Males: Days of incapacity	20·4 million
Females: Days of incapacity	6·2 million
Males 10% of days of incapacity	
Females 6% of days of incapacity	
Total deaths	36,985

of sulphonamides, penicillin and other antibiotics has done little to affect the mortality figures. Study of the social class incidence reveals a mortality in both sexes which is five times as great in social class V as in social class I (Fig. 1). The variation in mortality in

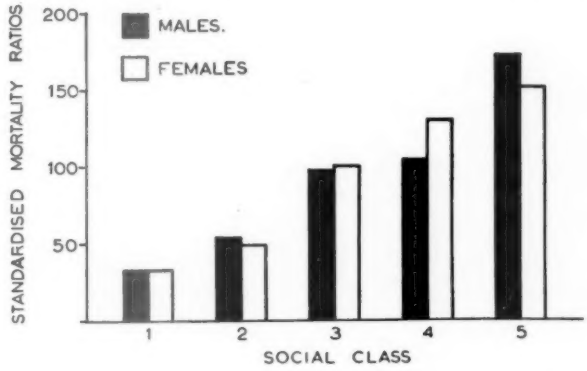

FIG. 1.—Standardized mortality ratio for bronchitis, men and women in England and Wales 1950.

comparatively young men is equally striking when different urban areas are compared. Table II shows that Salford has a mortality for men aged 45–64 which is six times as heavy

TABLE II.—DEATHS FROM BRONCHITIS PER 100,000 IN MALES AGED 45–64 YEARS, 1950–1952

Warrington ..	321	Hastings ..	51
Salford ..	319	Eastbourne	63
Oldham ..	302	Gt. Yarmouth	67
Dudley ..	299	Canterbury	74
		Coventry	80

as that of Hastings. Several factors are responsible for this, but housing and atmospheric pollution are extremely important. Fig. 2 is taken from a photograph supplied by Dr. J. L. Burn, the Medical Officer of Health of Salford, and shows something of the condition in

FIG. 2.—Photograph of ward in Salford 1955 where bronchitis morbidity and mortality are almost the highest in the country.

a ward of the city where bronchitis mortality and morbidity are highest. Despite much effort, atmospheric pollution from sulphur gases is getting worse in that city, while pollution from solid matter is falling. This is the tendency too in London, where fogs are becoming increasingly lethal. Surely an explanation can be found here in the increasing amount of coal burnt in the centre of our city by the great electricity and gas-producing plants. In a few years there was an increase of five million tons per annum in the coal used for these purposes within the London civil defence area. The Clean Air Bill will do little to abolish this menace, for it is aimed chiefly at the household grate, which contributes less than 10% of the sulphur in the atmosphere in many highly polluted areas.

The effect of smoking on initiating and maintaining chronic cough is slowly being realized. The tremendous increase of cigarette addiction revealed by a recent controlled investigation into the habits of those with chronic bronchitis showed that the majority had smoked more than twenty cigarettes a day for more than twenty years.

The life-history of the patient with severe bronchitis is one of the most pathetic stories in human ill-health. Years of increasing pulmonary insufficiency are punctuated by recurring bouts of "pneumonia" and "asthma", with sleepless nights and a cough which distends still further the emphysematous lungs.

One of my patients fell in the street on his way home from work in the fog of 1952. He was unable to climb the stairs to bed. He slept by the fire kneeling into an easy chair. Only in this way has he been able to sleep on many foggy nights since that time.

Bronchitis presents us with a challenge and also with opportunities in preventive medicine which we shall do well to seize in the next few years.

Section of General Practice

President—GEOFFREY BARBER, O.B.E., M.A., M.B.

[*January* 18, 1956]

DISCUSSION ON ULCERATION AND VARICOSE VEINS

Dr. L. Dulake (Reigate): Ulcerated legs and varicose veins are very common, causing an immensity of suffering and cost to the community in loss of activity.

We all know the typical case of varicose ulcer—more commonly a woman, in the late 40's onwards, often post-menopausal, multiparous, obese, with flat feet, hallux valgus, claw toes, corns, and osteoarthritis of both knees. Her countenance reflects the misery which drags her down all day; her ungainly gait, her heavy eyes from disturbed nights, her pasty anæmic complexion and dyspnœa, complete the picture. Her locomotory disabilities reduce her activity so that her obesity progresses. She has few pleasures in life, and her intelligence quotient is often low, so that eating is the only remaining satisfaction she can attain. Weight reduction, so important in the management of most of her disabilities, is extremely difficult.

She has usually attempted home treatment, involving the application of ointments, many containing carbolic, or liquid disinfectants. These in themselves have aggravated the condition, by inhibiting granulation tissue formation, and have often added a chemical dermatitis to the existing varicose eczema.

Daily dressings are applied by her on pieces of rag with the full panoply of septic kitchen technique, and a dirty piece of bandage holds it in place, her œdematous foot and ankle bulging below it, and her fat œdematous leg above it.

This picture is, however, only the end-result of neglect in one type of patient with varicose ulcer. The early ulcer, or pre-ulcerative state may be seen in people of very different general type. Young adults of both sexes, physically fit, and mentally alert present them, while another type of case which is not uncommon, is seen in the spare elderly individual, of good intelligence, without much evidence of large varicose veins, a history of thrombophlebitis in the past, the ulcer-bearing part of the lower leg or gaiter area being very much narrowed, pigmented and indurated. The ulcer has usually been present for very many years.

There is one feature common to all these types, and that is the site of the ulcer, which is over the lower end of the tibia on its medial aspect and posterio-superior to the medial malleolus. Less commonly an ulcer is found above and behind the lateral malleolus.

Differential diagnosis.—The commonest cause of ulceration in this country is undoubtedly the varicose or gravitational ulcer, but it is wise rapidly to run through the less common causes of ulcer in the leg. Any ulcer not related to the malleolar region, especially the medial one, and sited on the front of the shin or on the calf is unlikely to be varicose.

Syphilitic gummatous ulcer is usually over the shaft of the tibia, and its typical wash-leather base and relative painlessness are diagnostic, the complement-fixation test being confirmatory.

Tuberculous ulcers may be deceptive, and Bazin's disease, is, in my experience, less common than it was.

Ulceration of badly scratched lichen planus can resemble varicose eczema and ulceration, and I have seen ulcerated perniosis confused with varicose ulcers.

Ulcers due to arterial disease, as was recently pointed out by Cotton (1955), may be found in older patients. There may or may not be co-existent varicose veins. Absence of arterial pulsation in dorsalis pedis and posterior tibial arteries, calcification of the vessels of the leg demonstrated in X-rays, and hypertension, support the diagnosis. The site of the ulcers is often related to the malleoli in the typical sites of varicose ulcer.

Diabetic ulcers are trophic in nature, as are the ulcers associated with diseases of the nervous system.

In the tropics, ulcers of the leg are common. Diphtheritic ulcers can occur—in Bengal I saw a lot of them—and they are highly dangerous because they often carry a virulent strain of diphtheria.

Cutaneous leishmaniasis is common in Bengal and unless thought of, the reliable findings of biopsy can be forgotten.

Veldt sores containing low-grade pyogenic infections of various strains are also common in certain parts of the tropics.

Old-standing varicose ulcers may develop epitheliomata, while epithelioma with ulceration can occur on the leg as elsewhere, apart from varicose ulceration.

Pathology.—There is an unsatisfying acceptance of the purely mechanical notion that anything causing increased intra-abdominal pressure—particularly pregnancy, occupations involving prolonged standing, and deep thrombophlebitis—will cause varicose veins, when to my mind there must be other factors existing in the state of the vein and its anatomy.

Our knowledge of the pathology of the condition is increasing. Kinmonth (1950) points out that varicose veins histologically, far from showing a deficiency in elastic tissue and muscle wall, reveal no undue fibrosis in the media, while the muscle appears healthy and even hypertrophied, suggesting that the defect is a physiological one, either nervous or hormonal, causing relaxation of the muscle wall.

Cotton (1955) found that arteriograms showed rapid filling of veins in some cases of ulcerated legs and also occasionally in legs amputated for gross ulceration. In addition, he had demonstrated in casts of veins taken out by stripping, that the varices occur below the valves, and not above the valves, suggesting that a cause of the "blow-out" is due to increased pressure in a section of vein below a valve, eventually giving rise to incompetence.

This work throws new light on the problem. It would be interesting to know whether arteriovenous communications can be demonstrated in those families where massive varicose veins appear in several members of the family in the late teens and early twenties. These cases are often in males, of good physique, definitely not obese, while the girls are often concerned at the ugly appearance of the veins in an otherwise neat and healthy-looking body. Many of them have not indulged in athletics nor continued long enough at an occupation involving standing.

In performing the operations of ligation at strategic points, it is essential to identify the position of communicating veins with the deep set of veins, but this difficult estimate, based on careful study of the speed of filling of various sections of varicose vein after occlusion with elastic bands or with the finger, placed at strategic points, is not entirely reliable, because the communicating veins do not necessarily flow into the varicose veins, but into non-varicose tributaries. One doubts therefore whether the site of the communicating veins is relevant to the true pathology of this condition; otherwise, the undilated veins would be the varicose ones, and vice versa.

A personal observation which has raised my curiosity lies in the fact that at operation, the long saphenous vein in the groin is demonstrable as a large dilated vein, even though the patient has been lying in bed for perhaps a day, or at least some time on a stretcher, as I always operate under a general anæsthetic. One would expect this vein to be empty and collapsed after recumbency.

During the process of clearing the vein, and while tying the tributaries in this site, the saphenous vein is seen to contract rapidly till it is normal in size. The vein further down the leg, if exposed for ligation, is also vigorously contractile, and only in the lower leg where it is often closely adherent to the skin, is it papery, fragile and degenerate in quality.

This observation, which is supported by the histological findings mentioned earlier, raises in my mind the question as to whether there is a neurovascular defect in varicose vein production, and, bearing in mind how many disorders are being found, at least in part, to be psychosomatic in origin, whether varicose veins are developed in a vein which undergoes segmental spasm when it should relax, and relaxes when it should be contracting. Such a possibility would explain the development of raised intravenous pressure in segments below valves, which if the neurovascular control was normal, would permit the blood to flow upwards.

I have no supporting evidence for this idea, which is based purely on observing the active contractility of the vein, so long regarded as an inert overdilated tube. Manometric tests could, perhaps, be devised by those who are carrying out intensive work on this condition.

Ætiological factors in varicose vein production.—Familial and inherited tendencies suggest some congenital defect in anatomy or physiology. Occupations involving standing, athletics, and soldiering, and pregnancy itself, all appear to be related to the onset of varicose veins, but cannot be the fundamental cause, because where thousands doing these things have varicose veins, millions stand, run, serve in the Army and reproduce without them. Similarly, ulceration certainly follows a slight knock in certain people, but more often than not a small dark spot appears, crusts, separates, and behold! an ulcer. There is no history of injury, and often no history of thrombophlebitis.

The anatomy and physiology of varicose veins.—Kinmonth and Robertson (1949) state that the damage to valves was clearly demonstrated as a sequel to retrograde injection of sclerosing agents through a vein catheter. An accurate recognition was made of the distribution of sclerosing agents into unwanted sites by venography and the histological changes in veins produced by sclerosing agents were closely studied.

Lockhart-Mummery and Smitham (1951) pointed out that the patient with massive varicose veins of both long and short saphenous systems often had healthy elastic skin, while patients with induration, pigmentation, and contraction of the skin in the gaiter area, often had no obvious varices. They deduced that so-called varicose or gravitational ulcers are not directly caused by varicose veins. A series of venograhic studies showed that thrombophlebitis of the deep veins is followed by recanalization in about 90% of cases in two years, but that the valves, especially in the communicating veins, have been irretrievably damaged. They concluded that ligation of the deep veins would be a logical procedure, because ulceration appeared about the time that recanalization had taken place.

Moore (1954) made a further extensive venographic study, and also performed manometry of veins. The main points of his work were that in the erect posture, while standing still, the venous pressure at the ankle in a normal long saphenous vein is equal to that of a column of blood from the heart to the ankle; while on exercise, the pumping action of the leg muscles and the competence of the valves in the communicating veins produces a fall in venous pressure, on an average 45 mm.Hg. If there was incompetence of the valves, with a gravitational syndrome, the pressure actually rose on exercise. He correlated these manometric findings with venographic studies.

Muir *et al.* (1954) made a further venographic study correlated with clinical tests in the location of incompetent communicating veins and improved the accurate siting of venous ligations.

Cockett (1955) demonstrated the precise anatomy of three important perforating veins in the lower leg, which do not enter the long saphenous vein, but a longitudinally disposed vein posterior to it called the posterior arch vein.

Incompetence of the valves in these communicating veins is convincingly demonstrated as a cause of varicose ulceration, and the uselessness of ablating a normal long saphenous vein, which runs through the indurated and ulcerated area, is explained.

The important fact for a general practitioner lies in the proof that the valves are damaged by thrombophlebitis in communicating veins and that cure of ulcer can only be permanent if the condition is tackled early. Once shrinkage of tissues and chronic network of stagnant dilated venules has developed, cure is very difficult. Nevertheless, all this does not explain why some people develop varicose veins, and I find my mind reverting to the actively contracting and dilating object I see at operation. Surely the fundamental mischief must lie in the field of neurovascular disorder.

Methods of Treatment

The principle in treatment is to abolish the œdema and stasis underlying the condition, and to remove the entire system of varicose veins, or render them inert.

(1) *The Ulcer*

Bed rest is undoubtedly of great benefit in the treatment of varicose ulcer—indeed only a few days of recumbency will produce marked improvement, enhanced by raising the foot of the bed.

During this stage it is an advantage to clean the ulcer with hypertonic or normal saline compresses or Eusol. It is not wise to use greasy applications nor are antibiotics wise, especially on tulle gras, because of the risk of skin sensitization. Moreover the ulcers usually grow a mixed variety of infection, often including *B. coli*, *B. pyocyaneus* and other low-grade infections, besides streptococci and staphylococci.

As soon as ulceration is no longer progressing, the ambulatory stage can be embarked upon.

Dr. Stanley Rivlin will describe bandaging and other treatment in detail. Individual sensitivity to elastic adhesive bandages is a problem.

Bandaging with inelastic materials such as Unna's method, and the Viscopaste and Ichthopaste, is well tolerated by patients, but they have the disadvantage of giving no elastic support.

Besides Eusol and saline compresses, there are occasions when very troublesome ulcers appear to respond to dressing with gentian violet, scarlet red; and occasionally Priscol locally has been used in order to stimulate granulation tissue formation. Cockett himself employs entirely bland zinc cream.

It is an advantage to get the ulcer healed before embarking on surgical treatment of the

veins. A portal of entry for infection is a disadvantage when the risk of operation consists almost entirely in thrombophlebitis in deep veins and embolism therefrom.

The surgical measures necessary in the treatment of varicose ulcers may include excision of the ulcer bed and skin grafting, with pinch or Thiersch grafts on a healing ulcer bed.

We now have Cockett's operation added to these measures, the principle of which consists in excising the posterior arch vein through an accurately sited vertical incision, ligation of the communicating veins on the Trendelenburg principle at the point of emergence through the deep fascia, and excision of the ulcer with skin grafting delayed for a few days.

Last of all gross ulceration of long standing may necessitate amputation, particularly when epitheliomata have developed in the chronic ulcer.

(2) *Methods of Dealing with the Varicose Veins*

(i) Injection with sclerosing agents.
(ii) Ligations.
(iii) Vein stripping.
(iv) Elastic stockings.
(v) Bandaging.

In the past, extensive excision and long spiral incisions with ugly scarring of the legs have been practised.

Injection.—Injection treatment has only a temporary place and is not satisfactory in the treatment of large varicose veins. If carried out at all, the empty vein technique is essential. It should be reserved for the treatment of small varicose veins, injected in over-anxious patients for cosmetic reasons, and for "clearing-up" treatment after radical procedures.

Serial ligation.—I understand from Dr. Rivlin that Trendelenburg's operation as we know it, in which the saphena magna is tied at the junction with the femoral vein, after careful ligature of *all* the tributaries, is misnamed. The original Trendelenburg was a simple ligation. I use the name, however, to indicate the modern complete procedure.

This is an essential part of serial ligation and of vein stripping. An accurate estimate of the veins should be made; they should be marked, and an effort made to locate some, at least, of the communicating branches by placing elastic bands round the leg at various points and seeing how rapidly the vein fills on standing up, or an ambulatory test may be applied on the same principle to estimate the patency of the deep veins.

It is often necessary, or even usually so, to ligate the short saphenous vein.

There is no question that this type of operation offers a high percentage of improvement, if not cure. Ulcers certainly remain healed. But Cockett's work on the perforating veins and ulceration will, I feel sure, find an important place in surgery.

I have recently adopted vein stripping. Its place lies in the cure of massive veins without ulceration.

If injection therapy is to be done in general practice, it should be carried out at a small clinic in a group practice, or with all proper equipment at a special session in a single-handed practice. It should never be conducted on a rough-and-ready basis.

Palliative treatment.—Some varieties of elastic stockings are of little use as they are not sufficiently strong. The Lastex yarn two-way stretch type are best, though they can cause tiresome itching of the leg.

Careful bandaging with elastic or crepe bandages still has a place. The difficulty here is to teach patients how to apply them evenly and properly.

General health.—Obesity is one of the biggest obstacles to success. The kind of patient who has varicose veins, ulcers and eczema is so often a bad collaborator, that the war against fat is very difficult.

Anæmia, cardiac conditions, diabetes and avitaminosis are not to be overlooked.

There is no cure for varicose veins, but they can be kept under control. The chief obstacle to success, given a careful doctor, is the low intelligence of so many of the victims.

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Dr. Stanley Rivlin (London Varicose Clinic): This short paper will attempt to do no more than underline what we at the London Varicose Clinic believe to be important points in the treatment of *varicose* ulceration.

There is at the moment great confusion in describing chronic leg ulceration; a number of workers, finding that all ulcers are not due to varicose veins, have abandoned the terms "varicose" completely, substituting "venous" or "stasis" in their search for an all-embracing title. This does a great disservice to progress, for it is only by breaking down the ulcers into their various groups such as "varicose", "post-thrombotic", "arteriosclerotic", &c., that accurate prognosis, after-care, prevention of recurrence and comparison of results is made possible.

On this basis we define a *varicose* ulcer as one occurring on a limb which has no other pathology except varicose veins; furthermore *once this type of ulcer is healed and the varices properly dealt with, the patient can look forward to a normal leg for the rest of his or her life.* This last point is an important one for it applies to approximately 60% of all ulcerated legs. Post-thrombotic (post-phlebitic) ulcers on the other hand, accounting for 30% of the leg-ulcer statistics, do not carry such a confident prognosis, for although the patient can be kept ulcer-free it requires constant and unremitting care.

Varicose veins.—It is almost impossible to estimate what proportion of all patients with primary varicose veins eventually develop ulceration, for no one has yet followed up a large number of untreated cases to determine their ultimate fate. On the other hand it is relatively easy to forecast whether any individual patient is a candidate for ulceration, on the basis of the size and distribution of his varices, the presence of œdema, the occurrence of superficial phlebitis and the family history. There is no doubt that any patient in whom ulceration is likely, should be strongly advised to undergo surgical treatment for his varices, and it is also true to say that even where the skin is prognostically safe, operation is of the utmost value in permanently relieving the common symptoms exemplified by aching, tiredness, irritation, swollen ankles and nocturnal calf cramp.

But there is a widespread feeling, both amongst patients and their doctors, that the surgery of varicose veins is best avoided. This is an attitude of mind which I personally find quite understandable, though not necessarily justifiable, for it must be admitted that the results in the country as a whole are deplorable. This I believe to be due to the continual search for a blunderbuss operation which will deal with all types of varicose veins. At the moment the favourite is "stripping", and indeed in America they have just invented a hydraulic vein stripper. But we must remember that stripping, as now practised in this country, has been shown a failure in the United States. At the Mayo Clinic they now go much farther than a simple strip, and aim to excise or avulse every superficial vein in the leg through a large number of long incisions. And so the wheel has turned a full circle, for we are back to the 1930s.

There can no more be a satisfactory blunderbuss operation for varicose veins than there is for abdominal pain. Why is it then that whilst most surgeons are prepared to take time and trouble in examining an abdomen so as to achieve an accurate diagnosis, they are apparently quite satisfied to take one quick look at varicose veins and put them on the list for whatever happens to be the standard all-embracing procedure of the moment?

The surgical treatment of varicose veins requires a careful clinical examination[1] *to plan a specific operation for each individual case, instead of the present hopeful blunderbuss venous evisceration.*

Ulcerated legs.—Despite the fact that 60% of all ulcers are due to incompetent varices I firmly believe that it is quite wrong to treat varicose ulcers by operation upon the veins. This should be carried out *after* the ulcer is healed as a permanent prophylaxis against future recurrence. The reason for this is a purely technical one but it is also extremely pertinent for no less than 35% of all varicose ulcers referred to the London Varicose Clinic have had previous unsuccessful venous surgery, making re-operation after the ulcer is healed a difficult and tedious procedure.

One of the most important steps in any operation upon internal saphenous varices lies in the performance of a true juxta-femoral ligation, that is to say *absolutely* flush at the sapheno-femoral junction. Now this procedure can be quite difficult in the most uncomplicated cases, but if you can imagine the whole groin field full of fleshy, friable, hyperæmic glands often extending down to the femoral sheath—a typical finding in the presence of chronic ulceration—then you will realize why it may often prove impossible to carry the dissection right down to the femoral vein: and the moment the ligation becomes "high" as opposed to "flush" the whole operation is completely nullified, and indeed from the patient's point of view it were better not carried out at all. It is thus far better

[1] A short colour film demonstrated the technique used for locating the sites of primary venous incompetence.

to wait until the ulcer is healed and the glands have disappeared before moving on to surgery. For in any case even after operation the ulcer is still present and has to be treated by bandaging or rest. So why not heal it first and have a 100% chance of operative success, instead of operating first with a high rate of failure (Fig. 1A and B)?

FIG. 1A.

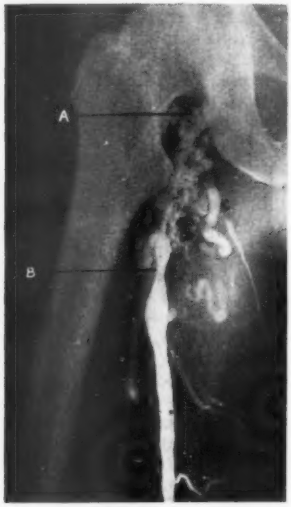

FIG. 1B.

FIG. 1A.—This man developed a *varicose* ulcer at age 23. He was treated by immediate operation upon his varices and during the subsequent rest in bed the ulcer healed (dark scar). Owing to the presence of multiple small inflammatory inguinal glands, a *true* juxta-femoral ligation was not performed. Within two years the veins recurred (upper thigh) and after five years further ulceration threatened.

FIG. 1B.—Confirmatory phlebogram showing (A) proximal stump of internal saphenous vein ligated at least ¼ in. from the sapheno-femoral junction; (B) distal stump of internal saphenous vein; (C) Medusa's head of dilated tributaries joining in the two stumps.

Treatment of ulcerated legs.—Almost every patient one sees has been brought up in the strict faith that "rest" is the keystone in the arch of ulcer healing. I am not referring to resting in the supine position on a bed whose foot is raised 9 in.; this can do nothing but good so far as the leg is concerned and is really the only other *certain* method of treatment as opposed to the ambulatory technique which I personally favour. *The type of "rest" which is so pernicious is that which encourages lack of use of the affected limb in an otherwise mobile patient.*

"Don't use your leg too much." "Sit down now!" "Put it up on chair." This is the constant exhortation wherever they go. Most of them succumb and "rest" all they can, for after all they can remember as children watching their mothers and grandmothers "resting" their bad legs. They still, however, have a sneaking feeling that rest is not the panacea it is thought to be for they find that no matter how large their ulcer, they *like* walking as much as they hate standing, whilst after sitting down "resting" their leg out on a chair in front of them it becomes stiff and set and painful. In fact as soon as one explains the principles of venous return in simple terms, using the comfort of walking, which they themselves have already experienced, as the pivot of the argument, they seize the essential facts immediately and become model ambulatory patients, keeping faithfully to the rules (Chart I) which they find on the back of their appointment cards.

Physiologically, "rest" does far more harm than good for, in interfering with the normal mechanism of tissue fluid interchange, it encourages œdema, the basic factor in the maintenance of almost all chronic leg ulceration. Fig. 2, redrawn from Best and Taylor (1950), shows the factors involved in the maintenance of tissue-fluid equilibrium; the most vulnerable of all is the hydrostatic pressure inside the venule, which in turn depends upon the hydrostatic pressure within the larger veins of the leg. Fig. 3, based on Walker's figures (1950), demonstrates the fact that the pressure in the leg veins in an ambulatory patient is

CHART I.—RULES FOR PATIENTS UNDERGOING "BANDAGE TREATMENT" (ELASTIC ADHESIVE AMBULATORY COMPRESSION) FOR ULCERATED LEGS.

These instructions are also of great value in the permanent care of patients with chronic œdema following a deep venous thrombosis

USE YOUR LEG NORMALLY WHILST UNDER BANDAGE TREATMENT

1 Avoid standing STILL, but if you have to be on your feet take a few steps whenever possible.
2 Wear Shoes, never Slippers, in the house. If your feet feel hot and tired at the end of the day, change into another pair of SHOES not Slippers.
3 Do not sit with your legs crossed.
4 Do NOT sit with your legs out in front of you on a stool.
5 Sit NORMALLY but move your ankles up and down (as if beating time to music) every now and again.
6 Walk as much as you please.
7 Do not sit close to the fire.

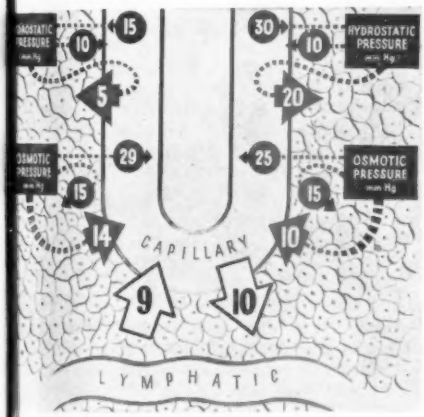

FIG. 2.

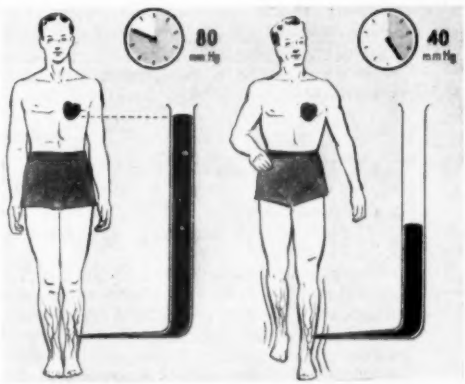

FIG. 3.—Effect of ambulation on venous pressure.

FIG. 2.—The hydrostatic pressure of the blood at the arterial end of the capillary (30 mm.), i.e. the force driving water and its dissolved crystalloids through the capillary membrane, is offset by the hydrostatic pressure of the tissue fluid on the outer side of the membrane (10 mm.). The net filtration pressure is thus 20 mm. (30 mm. — 10 mm.). On the other hand, the osmotic pressure of the plasma at the same point amounts to 25 mm. although this in its turn is offset by the osmotic pressure within the tissues (15 mm). The difference, i.e. 10 mm. (25 mm. — 15 mm.), acts as an attractive force to hold fluid within the vessels and so must be subtracted from the effective hydrostatic pressure of 20 mm. *The net result of these opposing forces will be a filtration of fluid through the vessel wall into the tissues under a pressure of* 10 *mm.* (20 mm. — 10 mm.). With the loss of water, the osmotic pressure of the plasma increases as the blood passes from the arterial to the venous side of the capillary, rising to 29 mm.: whereas that of the tissues remains fairly stable at 15 mm. There is thus a net attractive pressure within the capillary of 14 mm. (29 mm. — 15 mm.) The hydrostatic pressure of the blood at the venous end of the capillary is now only 15 mm. and as the tissue fluid pressure remains at 10 mm., the net filtration pressure is reduced to 5 mm. (15 mm. — 10 mm.). This, in turn, has to be balanced against the osmotic pressure of 14 mm., *leaving a net pressure of* 9 *mm. to return water and salts into the blood stream.* Of all these pressures, the hydrostatic pressure of the blood within the venule is the most labile and it can be seen that it only has to rise a comparatively small amount to reverse normal fluid return, with consequent œdema.

Fig. 2 is based on Fig. 12, p. 30, Best, C. H., and Taylor, N. B. (1950). The Physiological Basis of Medical Practice. 5th Edn. London. By kind permission.

FIG. 3.—The hydrostatic pressure in the leg veins at any given spot is always derived from the vertical distance between the right auricle and the point of insertion of the manometer needle, *irrespective of the presence or absence of varicose veins.* The physiological difference arises when the patient begins to walk. When the leg is normal the pressure will fall almost to zero, but even in the presence of varicose veins it is very significantly diminished on exercise.

almost utterly dependent upon the degree of active movement of the muscles, particularly the calf muscles as utilized in flexion and extension of the ankles.[1] This is why the patients are instructed to wear well-fitting shoes and not sloppy slippers, so that when they walk they use their ankle-joints in the proper way; and it is also the reason why we encourage them to "walk" even when sitting in a chair.

Conclusion.—Here then is the key to the successful treatment of leg ulceration by elastic adhesive ambulatory compression . . . it *must* be truly ambulatory. In bandaging the leg we squeeze out the œdema; but it is the patients, using their legs in a normal manner, who prevent further œdema from collecting and thus not only maintain the tissues of the leg in a near-normal physiological state from the point of view of wound healing, but also—and this is an important practical point—*keep the bandages beautifully comfortable.* Used thus, the method of treatment I have outlined[2] will heal ulcers in an average of twelve weeks and will be successful in nearly 95% of all cases, keeping the patients fully mobile doing their normal housework or earning their living during the whole period of treatment.

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[1]This point was demonstrated by means of a short film.

[2]The detailed technique of treatment involving the application of a *non-hardening* Dalzoband paste bandage, surmounted by a 3 in. non-standard Poroplast flexible adhesive bandage prepared to the specifications of the London Varicose Clinic, was demonstrated by means of a ten-minute colour film.

Mr. E. Troensegaard Hansen: I wish to make known the following observations as regards the treatment of cases of indolent ulceration in the proximity of the ankle. 6 known cases where ulceration had been present for over two years, which had failed to heal by the usual compression treatment, have been subjected to the following treatment at Charing Cross Hospital.

The patient was admitted to the hospital and the ulcer was cleaned and then scraped right down to deep fascia removing the skin edges. This was done under a general anæsthetic. Five days later the ulcers were amnion grafted. Six weeks later the dressings were removed and the ulcers were healed and have remained healed since. The follow-up treatment is extremely important. When the ulcer is healed a firm Viscopaste bandage is applied every three weeks for nine weeks then an elastic stocking, with a crepe bandage over it, is applied and this is worn for a further nine weeks. The result of this treatment is a healed ulcer, which remains healed, and there has been no breakdown in cases treated by this method.

The reason for maintaining compression for this period of time, after the ulcer has healed, is for the skin to become thick and solid over the ulceration site.

6 other cases were treated as out-patients by amnion grafting and the results were similar. These ulcers, however, were smaller, indolent, but the history was under twelve months. These again have remained healed, I am sure partly due to the careful post-healing treatment.

Twelve photographs before treatment and twelve photographs after treatment were shown and the merits of these results were discussed.

Section of Neurology

President—REDVERS IRONSIDE, F.R.C.P.

[*April* 5, 1956]

DISCUSSION ON MYASTHENIA

Dr. J. Hamilton Paterson (London): Credit for the first description of myasthenia gravis is often given to Wilks (1877) of Guy's Hospital and to Erb (1879), though Guthrie (1903) pointed out that Thomas Willis had described a patient with myasthenia gravis, judging by an account in his "De Anima Brutorum", published in Oxford in 1672 and translated into English by Pordage after Willis' death. Erb incidentally described the condition in 3 patients, 2 of whom he had seen in Friedreich's clinic at Heidelberg. He remarked on the liability of bulbar musculature to become involved, the frequency with which ptosis occurs and the progression of the condition by remission and relapse with a tendency to terminate in sudden death. In 1887 Eisenlohr and Oppenheim described single cases, as did Shaw three years later. They were concerned in differentiating myasthenia gravis from Duchenne's bulbar palsy as is indicated by the title to Shaw's paper in *Brain* in 1890—"A case of bulbar paralysis without structural changes in the medulla".

In 1893 came Goldflam's classical contribution. His close symptomatological analysis left little to be added subsequently. He pointed out that myasthenics became progressively weaker as the day advanced. He described the characteristic features of myasthenic weakness, noting that 20–30 movements involving affected muscles might reduce their voluntary response to zero. He stated that daily remissions and relapses were common but indicated that the former could last for up to four years. It was Jolly, however, who coined the current name for the condition for in 1895 he published his experiences with 2 patients under the title of "Myasthenia Gravis Pseudoparalytica", and described the myasthenic reaction obtained by repeated faradic stimulation of affected muscles. It is interesting to note that Jolly considered that myasthenia gravis was due to an abnormal condition of the muscles themselves.

By the time of Campbell and Bramwell's comprehensive review in 1900 there were some 60–70 cases on record. They noted that the muscles most likely to be implicated were those normally used most constantly, that weakness and even actual paralysis might persist after prolonged rest, and also that Jolly's myasthenic reaction to faradism might be unobtainable or but a passing manifestation. They considered that atrophy of affected muscles was altogether exceptional though they noted that it had been occasionally described. Campbell and Bramwell concluded that myasthenia gravis was probably due to a toxin acting upon either the axons of the motor nerves or their end-plates and interfering with their functional activity without causing structural changes.

Subsequently it became generally recognized that so-called myasthenic fatigability and persistent weakness were separate but often co-existent phenomena. It also became evident that actual muscle wasting was not so rare as Campbell and Bramwell had maintained; that cardiac muscles might on occasions be involved was suggested by some authors, while others showed that definite histological changes in muscle were occasionally to be found. Again, following on Weigert's discovery in 1901 of a thymoma in a patient dying from myasthenia gravis the importance of the thymus in the condition became increasingly evident.

In 1934 came Mary Walker's "scoop", the demonstration of the efficacy of physostigmine in the treatment of myasthenia gravis. This coincided with Dale and Feldberg's discovery

of the role played by acetylcholine in transmission at motor nerve endings in voluntary muscles, for they gave a preliminary report of their work at the May meeting of the Physiological Society in the same year. It is not surprising that those who held that myasthenia gravis was due to some defect in transmission at the myoneural junction were not slow to relate these two discoveries. Thus next year we find Hamill and Walker suggesting that the effect of neostigmine "seemed explicable on the hypothesis that in myasthenia gravis there is defective production at the nerve terminals of acetylcholine or some allied substance, and that under the influence of the drug destruction of this substance is delayed". From this approach stems one of the two main trends in research into the condition in the last two decades—that concerning the myoneural junction. The second trend—the role of the thymus in myasthenia gravis—received its main impetus at the hands of those who have demonstrated the undoubted value of thymectomy in the treatment of the disorder, but it derives from older considerations, as has been seen.

Diagnosis

Prior to the advent of neostigmine the diagnosis of myasthenia gravis could naturally be made on clinical grounds only, though the demonstration of Jolly's myasthenic reaction was occasionally of help. After 1934, however, the value of a test dose of neostigmine soon became apparent and a prompt response to this drug is considered diagnostic particularly if the clinical features of the case do not conflict with the diagnosis. Of course, on occasions clinically typical examples of the condition do not appear to respond to neostigmine; commonly in advanced cases, for example, there may develop a relative or seemingly absolute resistance to the drug. Again, but rarely, the clinical picture may be typical of myasthenia gravis yet the response to neostigmine is never other than equivocal. Rowland (1955) has recently described a good example of this state of affairs. On the other hand an alternative diagnosis may be considered if, despite myasthenic weakness responding to neostigmine in greater or lesser degree, there are clinical features which do not accord with the classical descriptions of myasthenia gravis, or if there is evidence to suggest the presence of some other disorder.

Myasthenia in Other Conditions

(1) *Thyroid disorders.*—There are quite a number of accounts in the literature concerning patients, most of whom were women in the middle decades of life, who apparently had classical myasthenia gravis as well as thyrotoxicosis. Millikan and Haines (1953) have reported 25 such cases, in the majority of which hyperthyroidism developed before or simultaneously with the onset of myasthenia. They estimated that approximately 5% of myasthenics might also develop thyrotoxicosis. Treatment of the latter seemed to relieve the myasthenia in some instances but in others it had no effect. On occasions, a so-called "see-saw" relationship between hyperthyroidism and myasthenia has been described in that the latter is apparently relieved by the onset of the former only to become worse when the thyrotoxicosis is treated. There have also been reports indicating that the weakness of chronic thyrotoxic myopathy may on occasions respond to neostigmine though, as McEachern and Ross (1942) pointed out, the myasthenic weakness in these patients is confined to the trunk and limbs, sparing muscles innervated by cranial nerves. Again there is that rare but dangerous condition termed by some "acute thyrotoxic bulbar palsy" or "myopathy", and by others "acute thyrotoxic encephalomyopathy". Laurent (1944) and Sheldon and Milnes Walker (1946) among others have reported examples responding to neostigmine, and, in the case reported by the latter authors, the trouble cleared up completely after thyroidectomy. It is not surprising that some uncertainty exists as to whether such patients have myasthenia gravis complicated by thyrotoxicosis or what has been termed thyrotoxic myasthenia.

(2) *Polymyositis and related states.*—Muscle weakness with or without demonstrable atrophy is, of course, the outstanding feature of the condition currently referred to as polymyositis but it is also encountered in the related states of dermatomyositis and systemic lupus erythematosus. This weakness on occasions responds to neostigmine. Reese and Harman (1954) and Christensen and Levison (1950) among other authors have noted this in relation to polymyositis. Bonduelle, Bouygues and Coulon (1955) describe two patients with dermatomyositis who had marked muscle weakness with fatigability of a myasthenic character which responded dramatically to neostigmine and Harvey *et al.* (1954) record neostigmine-responsive muscle weakness in systemic lupus erythematosus. It is interesting to note that Bonduelle, Bordet, *et al.* (1955) have also studied a patient with polymyositis who was found at autopsy to have a thymoma. In this instance neostigmine had no effect.

Here again the issue is somewhat complicated, for Störtebecker (1955) and others have described histological changes in the muscles of patients with apparently uncomplicated

myasthenia gravis which are indistinguishable from those seen in polymyositis and its related disorders.

(3) *Carcinomatous myopathy.*—Henson, Dorothy Russell and Marcia Wilkinson (1954) in their comprehensive review of carcinomatous neuropathy and myopathy recorded several cases with muscular fatigability and weakness responding in varying degree to neostigmine. Heathfield and Williams (1954) concurrently described another patient whose initial complaint of weakness of hip flexors and thigh muscles improved dramatically when he was given neostigmine, though he showed some features, notably loss of knee and ankle jerks, which are not typical of myasthenia gravis. Anderson, Churchill-Davidson and Richardson (1953), Mackenzie (1954), Shafar (1954) and Borelli and Kean (1954) have also reported patients with bronchogenic carcinomata who had myasthenia responding readily to neostigmine. A link between this group and the previous one is suggested by the known association of dermatomyositis with malignant disease though apparently none of the patients described in these reports showed any skin changes of note.

(4) *Nutritional disorders.*—In 1947 Denny-Brown drew attention to several rather obscure syndromes with myasthenic features which have been described in individuals suffering from prolonged dietary deficiency. A remarkable outbreak of this kind was recorded by Musselman (1945) and Katz (1946) in American prisoners in Cabanatuan. A group of patients, recovering from dengue in 1944, developed ptosis, diplopia and weakness of neck and facial muscles followed by dysarthria and dysphagia. The extremities were also involved in some. The condition responded promptly to restriction of salt intake and the addition of protein, potassium chloride and thiamine to their meagre rations. Katz also mentioned another group of war prisoners in the same camp who earlier had developed flaccid weakness of the arms and legs without cranial nerve symptoms. Their weakness responded rapidly to neostigmine.

Denny-Brown noted that a rather similar outbreak had been described in Japan in 1896 by Miura. This was known as "Kubisagari"—literally "one who hangs his head".

Histological Changes in the Muscles in Myasthenia Gravis

The literature on this subject is, in fact, quite considerable. It is generally assumed that Weigert was the first to describe in 1901 the lesions which Buzzard (1905) later called lymphorrhages. However, their prior description has been attributed to Glockner (1896) of Switzerland. Weigert (1901) was the first to associate myasthenia with a thymoma although he thought that the lymphorrhages he found were metastases from the thymic tumour. Subsequently lymphorrhages came to be thought pathognomonic of myasthenia gravis though more recently they have been demonstrated in a variety of disorders including Addison's disease, thyrotoxicosis and rheumatoid arthritis. However, Querido (1929) showed that these focal cellular accumulations in the muscle of myasthenics were not always exclusively composed of lymphocytes. His autopsy findings in an apparently typical case of myasthenia gravis were microscopically characterized by degeneration of myocardial and skeletal muscle with infiltration of these muscles by perivascular foci of leucocytes, lymphocytes, plasma cells and fibroblasts, associated with a marked increase in fibrous tissue in relation to these foci. He also found similar cellular accumulations in the liver, lungs and kidneys. Querido suggested that myasthenia gravis was a general vascular disease which could be defined pathologically as a chronic proliferating perivasculitis.

There have recently been quite a number of similar reports of muscle fibre degeneration of varying severity associated with cellular infiltration of an inflammatory character involving both voluntary and cardiac muscle. These include Professor Dorothy Russell's important contribution in 1953. It will be recalled that her findings were based on an examination of 8 consecutive patients, 4 of whom had thymomas. She classified her histological findings in the muscles into three types. In type I, representing the most acute changes, fibres undergo necrosis with resulting inflammatory cellular reaction and then disappear. Type II changes are characterized by a progressive atrophy of individual fibres associated with the formation of lymphorrhages in the later stages, while in type III only simple atrophy affecting single fibres or groups of fibres, having a different character to type II changes, is seen. Professor Russell found these three types of lesion to occur in a given striated muscle either singly or in combination. Often they were quite striking in the musculature of the tongue, palate, pharynx and upper œsophagus of patients who had bulbar myasthenia. Furthermore, she noted quite a close association between the histological changes and the clinical evidence of functional impairment, particularly in regard to the more severe abnormalities. The presence or absence of a thymoma did not appear to affect the issue, however. The myocardium was frequently involved, type I changes being found in 3 of the 6 cases in which the

heart was examined. Professor Russell concluded that these histological features, while not peculiar to or diagnostic of myasthenia gravis, were closely related to the muscular wasting and weakness encountered in her patients. Mendelow and Genkins (1954) described similar histological changes in 6 of 12 consecutive autopsies on myasthenics with or without thymomas. Myocardial changes of all degrees of severity up to marked necrosis were found in these 6 patients and were paralleled by similar changes in striated muscle elsewhere. All 4 patients with thymomas had myocardial lesions. Störtebecker (1955) has recently reviewed his muscle biopsy findings in 13 patients with myasthenia gravis. 6 of the 13 showed pathological features characterized by a varying degree of muscle atrophy with perivascular round cell infiltrations. He considered that these appearances were indistinguishable from those of polymyositis—a point to which reference has already been made.

The development by Cöers of a new biopsy technique of vital staining with methylene blue has afforded a new histological approach to the subject and has led to the demonstration of changes in the nerve endings in muscle which cannot be detected by the usual staining methods. Woolf *et al.* (1956) have recently studied a patient with myasthenia gravis in this way. A biopsy examination of one of the deltoid muscles showed changes in muscle fibres corresponding to Professor Russell's types II and III. The application of Cöers' technique demonstrated a striking abnormality of the sub-terminal motor fibres, the terminal arborizations and the terminal expansions of the intramuscular nerve endings. However, these changes are not pathognomonic of myasthenia gravis, and in other cases examined by this method the nerve endings have appeared normal (Cöers and Woolf, 1954). Woolf and his colleagues considered that in their patient the abnormalities may have depended on loss of contact of the nerve endings with the degenerated muscle fibres. This would explain why they have not been constantly found for it must not be forgotten that many cases of myasthenia gravis have been reported in which no histological changes in the clinically affected muscles have been noted.

Most of the available accounts of histological changes in the muscles of myasthenics have been based on autopsy examinations and such scanty information as they contain in regard to the neostigmine responsiveness of these muscles is often only related to the patients' terminal state. When accessible muscles are clinically involved more attention might profitably be paid to their histological appearances in life as seen in biopsy specimens. Such research might help explain why some myasthenic muscles respond initially to neostigmine, only to become resistant to this drug later on and why, on occasions, permanent weakness with or without demonstrable atrophy ensues.

Conclusion

Throughout this paper I have perhaps referred to myasthenia gravis as if it were a disease entity clearly to be differentiated from those other disorders which have been mentioned in which myasthenic weakness may be prominent. This differentiation, however, clearly breaks down at many points. Several writers have emphasized recently that myasthenia gravis is not an entity as such but is a syndrome of varied ætiology. Our ignorance as to its causation does not allow of the assumption that the same physiological disturbances are operative in every case. To attempt any elaborate classification without knowledge of the cause or causes of the syndrome will only add to the present confusion.

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Dr. H. C. Churchill-Davidson (Department of Anæsthetics, St. Thomas' Hospital, London): For many years the mechanism at fault in myasthenia gravis has fascinated both clinicians and research workers alike. It is generally agreed that the muscle weakness so characteristic of myasthenia shows many features that strongly resemble the interference with neuromuscular transmission due to *d*-tubocurarine. This has led many authors to search for the presence of a curare-like substance in either the thymus gland or the circulation of myasthenic patients. However, there are certain criteria that must be fulfilled if any such substance is to be deemed worthy of the term "curare-like". First, the neuromuscular block must be readily reversed by an anti-cholinesterase such as neostigmine or Tensilon; secondly, slow rates of stimulation must be better able to traverse the neuromuscular block than fast ones; and finally, although the muscle fibre may fail to respond to indirect stimulation through its motor nerve, it must at all times remain capable of contracting on direct stimulation. Up to the present time no extract from either thymic tissue or the serum of myasthenic patients has been found that can fulfil more than one of these criteria.

Much of the research into this condition has centred around attempts to assess the effect of acetylcholine on myasthenic muscle, but the extremely short duration of action of this substance has made the results difficult to determine. In 1948, however, Paton and Zaimis introduced a substance—decamethonium iodide (C.10)—which acted in a similar manner to acetylcholine but had the advantage that it was not rapidly destroyed by cholinesterase. The prolonged activity of this new drug made it possible for the first time to study the response of both normal and myasthenic muscle to an "acetylcholine-like" substance, and thus to remodel our theories of the underlying fault in this disease.

Before proceeding to a discussion on the significance of these results it is important to emphasize the general assumptions that are made regarding neuromuscular transmission in normal subjects. In 1936 Dale, Feldberg and Vogt initiated the theory of a chemical transmitter substance—acetylcholine—as responsible for bridging the gap between nerve and muscle. To date this has withstood the test of time. Briefly, when a stimulus reaches the end of a motor nerve, acetylcholine molecules are released. These rapidly pass to the receptor protein on the adjacent part of the muscle fibre (termed motor end-plate) and create a change in the electrical polarity—namely, depolarization. Depolarization of the end-plate is the signal that triggers off a similar response which passes in both directions along

the muscle fibre and is followed by a mechanical contraction. With acetylcholine the duration of depolarization of the end-plate, *in vivo*, to a single stimulus is but a fraction of a second, but after the administration of decamethonium the end-plate remains depolarized for ten to twenty minutes or longer. In other words, a depolarization block is present. *d*-Tubocurarine, on the other hand, prevents the acetylcholine molecules from gaining access to the receptor protein (end-plate), and thus blocks transmission of nerve impulses (non-depolarization block) until such time as the concentration of acetylcholine is permitted to accumulate—as occurs following the adminstration of an anti-cholinesterase or when finally the curare molecules are washed away into the general circulation.

There are, therefore, two fundamental types of neuromuscular block in man: depolarization block caused by acetylcholine and C.10 and non-depolarization block caused by *d*-tubocurarine. An essential difference between these two types of block is that an anti-cholinesterase—neostigmine or Tensilon—increases or does not alter a depolarization block, but will reverse one due to *d*-tubocurarine.

About six years ago, my colleague, Dr. A. T. Richardson, and I started to determine the effect of C.10 on the muscles of both normal and myasthenic subjects. At the outset we satisfied ourselves that our method using both electromyographic and volitional measurements gave consistent results in a group of normal volunteers.

When discussing the response of myasthenic patients to C.10 it is important to emphasize that there is a wide variation in the response of different muscle groups in any one subject. Notwithstanding this, however, two typical types of reaction may be high-lighted. First, there are those muscles which are resistant to the depolarizing action of C.10 and can tolerate doses three or four times that required to paralyse the muscles of a normal subject completely. At the other extreme, the muscle fibres rapidly become paralysed on the intravenous injection of decamethonium, but—in complete contrast to the normal subject—this weakness can rapidly be reversed by the administration of an anti-cholinesterase substance such as neostigmine or Tensilon. Briefly, these muscles first show some fleeting signs of a depolarization block before changing to that of the non-depolarization type—the so-called "dual response" (Churchill-Davidson and Richardson, 1953). This dual type of neuromuscular block is of particular importance because it can be seen in certain species of animals (Zaimis, 1953). For example, the muscles of the cat respond to C.10 in a similar manner to those of a normal subject, whereas the muscles of a myasthenic react like those of a dog or a monkey.

Further experimentation revealed that although decamethonium produced a dual type of response in myasthenic patients, it could be recovered unchanged from the urine of these patients. On the basis of these results we put forward the theory that the weakness of myasthenia gravis was not due to a circulating curare-like substance but to an alteration in the response of the motor end-plate to acetylcholine or one of its breakdown products (Churchill-Davidson and Richardson, 1953).

In 1955 Grob, John and Harvey published their findings on the effects of the intra-arterial injection of acetylcholine. Immediately following the injection there is a brief failure of muscle activity lasting about thirty seconds. About a minute after recovery has taken place the muscle fibre begins to show a secondary failure which, though not so severe, may persist for thirty minutes or longer. They found that the effect of the intra-arterial injection of choline—a breakdown product of acetylcholine—was identical with this secondary failure. Furthermore, although the injection of neostigmine enhanced the initial depression caused by acetylcholine in both normal and myasthenic patients, it increased the secondary failure in normal subjects but reversed the weakness in myasthenics. The inference is drawn, therefore, that acetylcholine acts in cases of myasthenia in two phases—an initial depolarization followed rapidly by a more prolonged non-depolarization block due to its breakdown product, choline. In other words, the dual response.

These results are complementary to our own using decamethonium in myasthenia, and together they provide convincing evidence that the mechanism at fault is an alteration in response of the motor end-plate.

I should like now to consider the value of decamethonium as a clinical test for the presence of the myasthenic syndrome. The basis of the test is to stimulate the ulnar nerve supramaximally at a rate of ten times per second and then to record the resultant integrated action potential on a cathode-ray oscillograph. In normal subjects a total dose of 2·5 mg. is sufficient to reduce the height of the action potential to one-fifth of its normal size, whereas in the myasthenic patient there is a negligible change.

If the myasthenic weakness is generalized the administration of decamethonium may so increase the paresis that it is no longer possible to give the full test dose. However, in such an instance 10–15 mg. of Tensilon intravenously brings about an almost instantaneous but temporary reversal of the weakness in cases of myasthenia.

It is important to emphasize that in our series of 42 cases a positive response to this test is specific for myasthenia gravis. We have investigated a number of cases in which the diagnosis of myasthenia was difficult when based solely on clinical grounds or on the response to neostigmine: in each of these cases the response to C.10 has made it possible to arrive at a definite conclusion. As a diagnostic test it is superior to neostigmine because some cases may fail to show a convincing recovery with the latter drug; it is of particular value, however, in distinguishing an hysterical from an early myasthenic weakness.

Again, this test has been found to be useful in investigating other allied conditions with a muscle weakness which has been reported at various times to respond to neostigmine. For example, we have examined 7 cases of dermatomyositis and 2 cases of thyrotoxic myopathy but failed to find a positive response. However, in 3 cases of carcinoma of lung and 1 case of thyrotoxicosis—each without a skin rash or wasting—we were able to detect the presence of this myasthenic change. Clearly much more work needs to be done before any conclusions can be drawn from these results.

The value of thymectomy in the treatment of this condition is controversial. However, we have examined 5 patients before operation and for periods from three and a half to five years after the removal of the thymus gland. Each case gave a positive result pre-operatively and despite the fact that 2 of these cases are now in a complete remission and must be classified as a clinical cure, the positive response has persisted in every patient. Furthermore, in 15 other cases—tested after thymectomy had been performed—the response was positive.

There still remain many features of the dual response in myasthenia that require further study. For example, is this change present in close relatives and offspring? Again, does a patient who has once shown a positive response ever revert to normal?

Reviewing our results to date using decamethonium we are tempted to speculate on the natural history of myasthenia. It would seem most convenient to divide the response into three stages. The first is the *resistant* phase wherein the muscle fibre can withstand far larger doses of decamethonium than normal without undergoing depolarization. Such a response cannot be recognized clinically because these muscle fibres do not show any signs of weakness. Examples of this group are best seen in the limb muscles of cases of ocular myasthenia. In the second group are those muscle fibres which show evidence of the *dual response*. The onset of this phase is characterized by the appearance of clinical weakness and there is evidence that the response of a particular group of muscles can freely interchange between these two phases. As yet, however, we do not have evidence that a muscle fibre in the resistant phase can return to a normal response. The third stage is termed *refractory* because here the muscle fibre fails to respond to neostigmine and wasting may become a prominent feature. The best examples of this group are usually to be found in cases of long-standing myasthenia, but this does not preclude the possibility of its occurrence in those patients with a recent history of muscle weakness.

The problem of the underlying mechanism of myasthenia still remains, but the conception of an alteration in the response of the motor end-plate can explain almost all of the clinical features. The fact that a similar type of response to decamethonium in myasthenia can be found in certain species of animals gives us hope that it will not be long before someone can demonstrate the cause of this change and that the secret of myasthenia will then be revealed.

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Dr. John A. Simpson (Gardiner Institute of Medicine, University of Glasgow):

The Value of Thymectomy[1]

Though seventeen years have passed since Blalock re-awakened interest in the role of thymectomy in myasthenia gravis, the value of the operation is still debated. Dr. E. A. Carmichael suggested that I should make an independent assessment of the National Hospital series. Sir Geoffrey Keynes invited me to extend the survey to include all patients operated on by him at New End and St. Bartholomew's Hospitals. As a control series those patients attending the National Hospital since 1934 with a diagnosis of myasthenia gravis were reviewed.

[1]A more complete account will be published elsewhere.

The diagnosis was made by the staff of the National Hospital and by other members of the Association of British Neurologists. I examined the majority of the survivors of both series; a few patients were questioned by post. I have adopted the role of devil's advocate to avoid the chance of introducing a bias favourable to the operation. This should be borne in mind when assessing the figures to be presented as they deliberately show the operation in what I believe to be the worst light. Patients were classified at follow-up examination according to the following criteria which are based on those used by Ross (1952). The essential feature is an assessment of change of status from the pre-operative state or the state on first admission to hospital in the control cases. Hence a patient with little disability does not qualify for a high category if this state is not significantly better than at the datum point. In case of doubt a patient was assigned to the lower category. It will be seen that any bias has been deliberately applied in a sense adverse to the operation.

Categories.—A. Full working life with no restrictions. No Prostigmin. No subjective weakness (small degree of permanent objective weakness permitted). Markedly different from pre-operative state.

B. Full life; minor symptoms not requiring Prostigmin or completely controlled by not more than 60 mg. daily. Significantly better.

C. Full life with few restrictions. (*a*) demonstrable myasthenia but not requiring Prostigmin; (*b*) still requiring drug but at least 40% less than before and with improved response.

D. (*a*) Improved but on same or greater dosage.
(*b*) Unimproved—irrespective of dosage.
(*c*) Worse.

Altogether 404 cases were available for study. Of the 270 female cases 11% had thymic tumours, and 13% of the 134 males. The higher age of onset and poor prognosis of these patients was confirmed and they will not be further considered here. The non-tumour cases (241 females and 116 males) showed a remarkably "normal" distribution curve for the age of onset which does not suggest that myasthenia gravis was diagnosed in a heterogeneous collection of unrelated diseases.

The operated series (182 females, 76 males) showed certain differences from the control series (59 females, 40 males). The former contained a preponderance of females at all age groups, the sex ratio varying from 4·5 : 1 in cases starting in the first decade to 1·1 : 1 in cases starting in the fifth decade. In the control series the sex ratio was even except in the 20–40 age group where females were in excess, and in the sixth decade where males outnumbered females. The two series were comparable for patients starting in the third decade and so the results of the whole comparison have been checked in this group but otherwise it has been thought advisable to compare the sexes separately. There was a statistically significant difference in the mean age at onset between the operated and not-operated series (the latter being nine years older at onset in both sexes). The standard error of the mean of the un-operated series was, however, much greater than that of the operated series. Possibly the early history of the thymectomy series has been more fully documented or the size of the sample is too small in the not-operated series. The mean survival from the first symptom was the same in the two series—females 13·0 and 14·7 years, males 12·5 and 12·4 years (the operated series is the first figure).

Results

The percentage of each series in each category at follow-up is shown in Table I. Two

TABLE I.—CLASSIFICATION AT FOLLOW-UP

Category	Not-operated		Operated	
	F %	M %	F %	M %
A+B	20·3	22·5	34·6	30·3
C	15·3	7·5	22·0	23·7
D	13·5	25·0	19·2	19·7
Data incomplete ..	15·3	22·5	7·1	5·2
Myasth. deaths ..	28·8	20·0	7·7	11·8
All deaths*	35·6	22·5	17·0	21·1

*Including post-operative death or deaths from unrelated causes.

differences are apparent between the operated and not-operated series: (i) in each sex all survival categories are increased and the deaths from myasthenia are reduced, (ii) there is no

marked difference between the sexes in the operated series. The significance of these conclusions is tested in Tables II and III. The higher proportion of patients in the A+B

TABLE II.—SIGNIFICANCE OF DIFFERENCE BETWEEN SERIES

Category	Female		Male	
	Difference*	S.E. of difference	Difference*	S.E. of difference
A+B	+14·3†	6·3	+ 7·8	8·4
C	+ 6·7	5·6	+16·2†	6·4
D	+ 5·7	5·3	− 5·3	8·2
Myasth. deaths ..	−21·1†	6·2	− 8·2	7·3
All deaths	−18·5†	6·8	− 1·4	8·1

* % in Operated series minus % in Not-operated series.
†Unlikely to occur by chance.

TABLE III.—SEX DIFFERENCE IN EACH SERIES

Category	Not-operated		Operated	
	Difference*	S.E. of difference	Difference*	S.E. of difference
A+B	− 2·2	8·4	+ 4·3	6·3
C	+ 7·8	6·2	− 1·7	5·8
D	−11·5	8·1	− 0·5	5·4
Myasth. deaths ..	+ 8·8	8·6	− 4·1	8·2
All deaths	+13·1	9·0	− 4·1	5·4

* % Females minus % Males in each series. The sex difference is not statistically significant in either series but the trend is reversed.

category, and the decrease in deaths due to myasthenia are greater than can be explained by chance in the female sex. This level of statistical significance is not reached in the males but the trend is the same (Table II). Slightly more women than men are in category A+B after operation and fewer women than men died of myasthenia. The analysis (Table III) shows that this could have occurred by chance but it should be noted that this represents a reversal of the trend found in the un-operated series where females had a slightly poorer prognosis than males. These data may be summarized in the statement that the status at follow-up examination of the two sexes is not significantly different but that the females have more to gain from operation—a prognosis slightly poorer than the male in the not-operated series being changed to a slightly better prognosis in the operated series, the change being greater than can be explained by chance. This conclusion reconciles the apparently conflicting statements of Keynes (1949) and Schwab and Leland (1953).

The extent of the improvement due to thymectomy may seem disappointing. It must be re-emphasized that this represents the minimum estimate of the distribution of categories. There are fewer deaths due to myasthenia (and indeed fewer deaths, even including the operative risk) and the survivors show a general "shift to the left". It must not be forgotten that the method of assessment makes little allowance for the magnitude of this shift. It does not give any indication of the patient, bedridden for years, who becomes able to resume a normal life after his thymus is removed. This could be indicated only by a method of comparison of grades of severity. This was not used in the present study owing to its retrospective nature and because of the difficulty of maintaining standards over the long periods involved.

Further analysis shows that the age of onset does not differ significantly in the different categories, but Keynes' (1949) statement that the best results are obtained in patients with a short pre-operative duration of myasthenia is confirmed (though statistically significant in females only). The follow-up period is comparable for all categories and there is no significant difference in their pre-operative requirements for Prostigmin.

Possible factors in the sex difference described above may be (i) thyroid abnormality was twice as common (18%) in women as in men (60% of the abnormalities noted were non-toxic); (ii) involvement of bulbar muscles at the onset was twice as common in women and initial weakness restricted to the extra-ocular muscles was more common in men; (iii) myopathic changes were twice as common in men as in women.

Electromyographic studies were presented to show that myopathic changes are common in myasthenia gravis without wasting and that the wasted muscles show changes indistinguishable from myositis. Lundervold's (1954) observation that myasthenic "fatigue" may involve derecruitment of motor units rather than decrement of individual units was confirmed. It was suggested that the evidence of electromyography and of histology as described by

Dr. Hamilton Paterson shows that the pathological changes of myasthenic muscle are not confined to the neuromuscular junction.

Acknowledgments

The kind permission of the Medical Committee of the National Hospital and of Sir Geoffrey Keynes to examine their patients and of the Medical Committees of St. Bartholomew's and New End Hospitals to scrutinize their records are gratefully acknowledged. Dr. E. A. Carmichael provided the facilities and gave invaluable advice throughout the investigation.

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[*June* 1, 1956]

COMBINED MEETING OF THE SOCIÉTÉ BELGE DE NEUROLOGIE AND THE SECTION OF NEUROLOGY

Chairman—Dr. REDVERS IRONSIDE
President of the Section

PROGRAMME

MORNING SESSION: Royal Society of Medicine.

Meningiomas of the Lateral Recess.—J. DE BUSSCHER, A. DE HAENE and G. HOFFMANN (Ghent).

Clinical and Pathological Manifestations of Cysticercosis in the Posterior Fossa.—E. R. BICKERSTAFF (Birmingham).

Familial Hereditary Cerebellar Ataxia with Oculomotor Paralysis.—F. DEVOS (Antwerp).

Control of *Petit mal* Attacks by Acetazolamide.—F. L. GOLLA (Bristol) and R. SESSIONS HODGE (Taunton).

Subacute Encephalopathy with Mental Disorder and Myoclonus. A Report of Three Cases.—J. D. SPILLANE (Cardiff) and W. MCMENEMEY (London).

AFTERNOON SESSION: National Hospital, Queen Square.

Chairman—Dr. L. MASSION-VERNIORY
President of the Société Belge de Neurologie

Spinal Cord Lesions due to Cervical Disc Arthrosis.—P. VAN GEHUCHTEN (Brussels) and A. DERAYMAKER (Louvain).

Symptoms of Internal Carotid Artery Thrombosis.—P. C. P. CLOAKE (Birmingham).

Combination of Diffuse Sclerosis and Familial Cerebellar Atrophy.—L. VAN BOGAERT and C. M. POSER (Antwerp).

The Surgical Results of Fifty Cases of Anterior Cerebral/Communicating Artery Aneurysms.—VALENTINE LOGUE (London).

[*June* 2, 1956]

Visit to the Department of Neurology, Radcliffe Infirmary, Oxford.

Section of Medicine

President—G. E. BEAUMONT, M.A., D.M., F.R.C.P., D.P.H.

[*April* 24, 1956]

DISCUSSION ON SARCOIDOSIS

Dr. J. G. Scadding:

The first difficulty which confronts us in discussing sarcoidosis is that of definition. Many authors of reviews of the subject have side-stepped this difficulty by starting with a historical review of the gradual development of the concept of sarcoidosis as a systemic disorder, which they substitute for any attempt at formal definition. There are only two generally agreed common features between such diverse conditions as the skin lesions described by Hutchinson (1877), Besnier (1889) and Boeck (1899, 1905), the pulmonary changes described by Schaumann (1914) and others, the eye lesions by Heerfordt (1909), the bone changes by Jüngling (1919), the frequent lymphadenopathy, hepatomegaly and splenomegaly, and the rarer changes in the kidneys, in endocrine glands, in the central nervous system, the mucosæ of the respiratory and alimentary tracts and elsewhere; these two common features are the frequent concurrence of two or more of these manifestations, and a common histological pattern. Accordingly, only these two features can be mentioned in the definition. I suggest the following:

Sarcoidosis is a disorder which may affect any part of the body, but most frequently the lymph nodes, liver, spleen, lungs, skin, eyes and small bones of the hands and feet, characterized by the presence in all affected organs or tissues of epithelioid cell tubercles, without caseation, with little or no round-cell reaction, becoming converted in the older lesions into a rather hyaline featureless fibrous tissue. Even though it may be stated quite correctly as an addendum to the definition that, at present, knowledge of the cause or causes of sarcoidosis is incomplete, the inclusion in the definition itself of the statement that "sarcoidosis is a disease of unknown ætiology" (Ricker and Clark, 1949) leads to logical difficulty; for if, as may well be the case, sarcoidosis can be caused by more than one agent, the discovery of one of them would involve the elimination of the group of cases caused by it from the category "sarcoidosis" so defined. Accordingly, no statement whatever about ætiology can be made in the definition.

The clinical manifestations of sarcoidosis are so numerous that it is difficult to obtain a reliable assessment of the frequency of involvement of various organs and tissues; every series is biased, both by the interests of the person observing it, and by the criteria which he adopts for diagnosis. My own series naturally contains a high proportion of patients with prominent intrathoracic manifestations. I have analysed certain aspects of the 142 cases of sarcoidosis which I saw first between 1938 and December 1955. Fig. 1 shows the reasons for which these patients first came under medical care. The high proportion of those whose disease was first discovered as a result of routine radiography, or because of respiratory

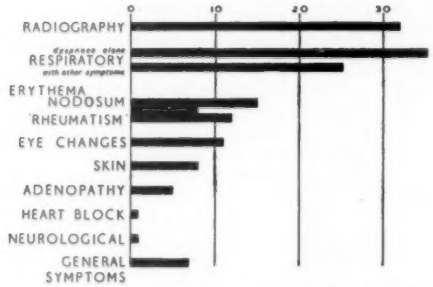

FIG. 1.—Earliest manifestations in 142 cases of sarcoidosis. "Radiography" indicates those patients who were symptom-free when routine radiography revealed abnormality in the lungs or hilar lymph-nodes. The "bridge" between "erythema nodosum" and "rheumatism" indicates the 8 patients who had both these manifestations concurrently.

symptoms is almost certainly a reflection of my known interests. The group whose first symptom was erythema nodosum or "rheumatism" is of some interest. There were 19 of these; 8 had both erythema nodosum and rheumatism, 7 had erythema nodosum alone, and 4 rheumatism alone. The good prognosis of these cases is worth emphasizing. Of 14 who were first observed long enough ago to permit an estimate of the outcome, 11 are well with normal chest radiographs, and 3 have only very slight residual disability. 17 of them had bilateral hilar lymph-node enlargement without lung shadows when they were first seen, and most patients presenting with this radiological finding do well.

The age and sex distribution of these 142 cases is shown in Fig. 2. The ages recorded are those at which the first detected manifestation appeared; e.g. if a patient had an iridocyclitis at the age of 22, and was seen by me with lung changes at the age of 27, he is recorded in the 20–25 year age group. There is no difference in age distribution between the sexes, but there are rather more females (78) than males (64).

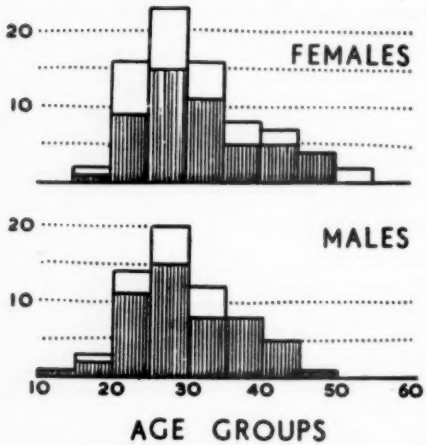

FIG. 2.—Age at apparent onset in 142 cases of sarcoidosis. The ages recorded are those at which the earliest manifestations were detected.

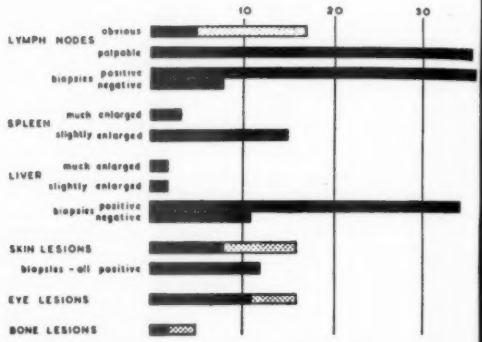

FIG. 3.—Clinically observed extrathoracic manifestations in 142 cases of sarcoidosis. The cross-hatched areas represent the cases in which lymph nodes, skin, eyes and bones became involved while the patients were under observation after the diagnosis had been established.

Fig. 3 shows the clinically observed extrathoracic manifestations in this series. Biopsy confirmation of the diagnosis was obtained in 101 of the 142 cases; it was obtained first from lymph-node biopsy in 39, from liver biopsy in 35, from biopsy of skin lesions in 12, and from biopsy of bronchial mucosa in 5. Other sites from which histological evidence was obtained included 2 infiltrated scars, 3 subcutaneous nodules, an infiltrated nasal mucosa, and a nodule in the breast. Biopsy of the lung and of hilar nodes at thoracotomy and of the liver at laparotomy were each responsible for confirmation in one patient. When superficial lymph nodes are palpable, they offer the most favourable available tissue for biopsy; 39 out of 46 nodes removed, or 85%, have shown specific changes. My experience with liver biopsy has been similar to that of others; 35 out of 46, or 76%, of those performed in patients eventually accepted as suffering from sarcoidosis having proved confirmatory. The relative rarity of notable enlargement of the liver and spleen and of the bone lesions of the hands and feet is noteworthy. The request for radiographs of the hands, in the hope that they will provide evidence of sarcoidosis in obscure cases, has always in my experience proved futile. Only 2 patients had changes in the bones of the hands when I first saw them, and both of these had also obvious skin lesions; in 3 others, radiographic changes appeared in the bones while they were under observation after the diagnosis had been established.

Intrathoracic manifestations.—I have prepared a summarized account (Fig. 4) of these in 102 cases which I have followed for not less than two years; the period of observation extends up to a maximum of fourteen years, though few cases have been followed more than seven years. The cases are grouped according to the radiographic changes when I first observed them. Of 16 patients who had enlarged hilar nodes at that time, 15 now have normal chest radiographs, and only one has slight residual radiographic abnormality; all are symptom-free. 6 of them developed diffuse mottling in the lungs before final resolution. Among the 32 patients who, when I first saw them, had both enlargement of hilar nodes

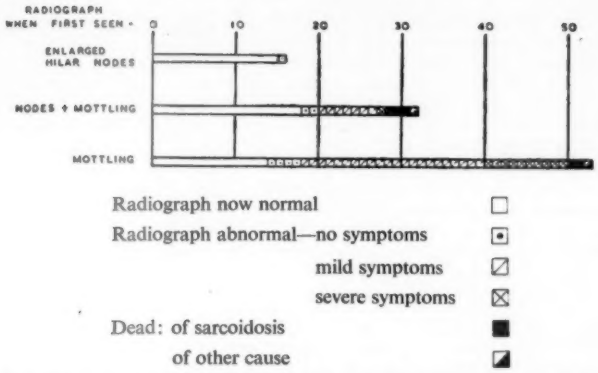

FIG. 4.—Lung and hilar lymph-node changes in 102 cases of sarcoidosis, followed not less than two years, grouped according to the radiographic changes at the beginning of the period of observation.

and mottling in the lungs, or who had diffuse mottling at that time with earlier radiographic evidence of preceding hilar node enlargement, 18 have resolved completely and are well, 2 still have some residual radiographic abnormality, but are symptom-free, 7 have mild symptoms, 1 has severe symptoms, 3 have died of sarcoidosis, and 1 of unrelated disease. Among the 53 who had generalized mottling of the lung fields when I first saw them, and in whom there was no record of previous enlargement of hilar nodes, the course has been even less favourable. 14 are well, with normal radiographs, 4 have some radiographic abnormality but no symptoms, 22 have mild and 10 have severe symptoms; 2 have died of sarcoidosis and 1 of an unrelated disease. There seem to be two possible explanations of these observations. One is that there are two distinct groups of cases of pulmonary sarcoidosis; one starting with hilar lymph-node enlargement and liable to proceed later to diffuse lung involvement, but in any case having a strong tendency to spontaneous resolution; and the other starting with diffuse lung involvement and tending to lead to fibrosis. The other possible explanation is that the patients who, when I first saw them, had diffuse lung involvement represented the residue of a very much larger group who had in the past had symptomless and undetected hilar lymph-node enlargement. I have no evidence to suggest which of these two explanations is correct. It remains a fact of immediate clinical importance that patients first coming under observation with enlarged hilar lymph nodes only can be given a generally good prognosis, and that there is no indication, as far as I can see, to use cortisone or corticotrophin in an attempt to modify the course of the disease at this stage.

Fig. 5 shows the tuberculin sensitivity in the 140 of these 142 cases in which it was

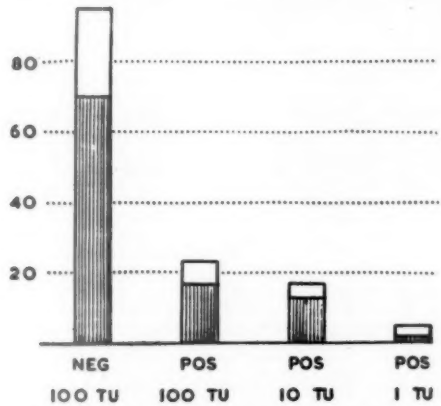

FIG. 5.—Tuberculin sensitivity in 140 cases of sarcoidosis (intradermal test with old tuberculin or P.P.D.).

precisely recorded. In the other two (both early in the series) the Mantoux test was recorded as "negative" without a note of the dose of tuberculin used. 68% were negative to 100 T.U., and the proportion is the same whether or no cases without histological evidence are included. This proportion is, of course, much higher than would be found in a group of the same age-distribution in the general population. It is also much higher than was found by my colleague, Dr. Clifford Hoyle, either in his own series of cases of sarcoidosis, or in a series of cases of Hodgkin's disease (Hoyle *et al.*, 1954). It is clear that the negative Mantoux test in sarcoidosis does not necessarily represent complete absence of tuberculin sensitivity; in some cases with negative Mantoux tests, reactions to tuberculin can be elicited by cortisone, either systemically or locally (Pyke and Scadding, 1952), or by using a depot tuberculin (Seeberg, 1951). It is perhaps significant that when tuberculin tests are done routinely in patients with established pulmonary tuberculosis, a few cases will be found to produce no reaction even to 100 T.U. I have records of several such cases, and a series of 11 has been reported by Mascher (1951).

There is no certain knowledge of the ætiology of sarcoidosis, or even of whether it forms an ætiologically homogeneous group. Controversy about its relation to tuberculosis continues. My own opinion is that the condition as seen in this country is a variety of tuberculosis. Of the 142 cases which I have analysed, no fewer than 14 have produced tubercle bacilli at one time or another. Bacilli were found in sputum, gastric contents or laryngeal swabs in 10 of them while they were still in a "sarcoid phase", in 7 on culture, and in 3 on direct microscopy only; in one of the latter, tubercle bacilli were subsequently cultured from lung tissue *post mortem*. In these 10 patients there was no change in the clinical or radiological picture at the time the bacilli were found; the Mantoux test was, and remained, negative to 100 T.U. in 8 of them, negative to 10 T.U. but positive to 100 T.U. in one, and positive to 10 T.U. in one. In one patient, tubercle bacilli had been cultured from a cervical adenitis four years before the sarcoid phase began. In 3 patients, the finding of tubercle bacilli in the sputum was accompanied by a change to a frankly caseating phase with development of tuberculin sensitivity. The existence of intermediate cases between caseating tuberculosis and sarcoidosis is another important piece of evidence; it has seemed to me quite arbitrary where the dividing line between these two categories should be placed, so that I believe that there is not in fact a clear division.

The usual failure of antibacterial treatment to produce any readily observable effect in sarcoidosis does not disprove this view, since the very indolent type of tuberculosis which is accompanied by low tuberculin sensitivity also may not respond in any obvious way to antibacterial drugs. Similarly the response which is often observed to cortisone cannot be used as an argument against a tuberculous ætiology, since in a number of cases of indolent tuberculosis, an immediate response to cortisone, combined with antibacterial drugs, may be observed. While thus expressing my opinion that sarcoidosis in this country is usually due to tuberculosis, I try to keep an open mind about the possiblity that some cases may be due to other causes, and that in other parts of the world other causes may even be more frequent; and the definition which I have suggested allows for this possibility, by imposing no logical bar to the addition of an adjective indicative of ætiology to the term sarcoidosis if the evidence justifies it.

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Dr. Peter Kerley:

The sarcoid granuloma has now been described in a wide variety of infectious diseases (bacterial, viral, fungoid and protozoan) in benign and malignant neoplasms, in occupational and collagenous diseases and in blood dyscrasias. It is accepted that it is a non-specific allergic tissue reaction to a great variety of agents so its finding by no means establishes a firm diagnosis of the systemic disease known as Boeck's sarcoidosis. The real incidence of systemic sarcoidosis is unknown but I would estimate that for every case presenting with symptoms, there are at least 5 detected by mass radiography without symptoms. Sarcoidosis has only recently been included as an entity in the mass radiography classification for England and Wales. Although detailed figures are not yet available, it appears that between four and five hundred cases per annum are being discovered.

The commonest initial finding is symmetrical enlargement of the bronchial glands and, for some unknown reason, the hila often swing outwards, even in the early stages before there is any fibrosis to pull them out (Fig. 1). This symmetrical splaying of the hila is often permanent and is a useful diagnostic point. The paratracheal and bifurcation groups are less frequently involved and very large mediastinal tumours are unusual. I have only once seen a glandular mass which was strictly unilateral and remained so.

The glandular stage may remain the only manifestation and may disappear quickly or persist for years. The shortest period I have seen is two months and the longest eight years. Pulmonary and systemic spread usually follow the glandular phase but occasionally iritis or uveo-parotid fever precede the intrathoracic lesions.

The relationship between sarcoidosis and erythema nodosum has been firmly established by Löfgren and in his series of 212 cases there was a remarkably high incidence in young pregnant women. In 3,000 routine antenatal X-rays last year I found 3 cases, 2 with glandular enlargement alone and 1 with glandular enlargement and pulmonary infiltration. In 1 pulmonary lesions spread during the pregnancy and have persisted unaltered after the birth of the child.

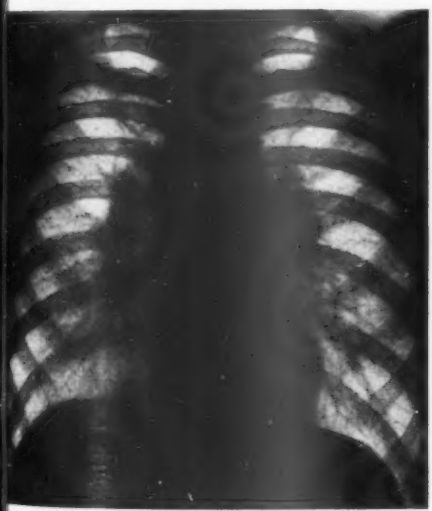

FIG. 1.—Splaying of the hila with glandular enlargement in sarcoidosis.

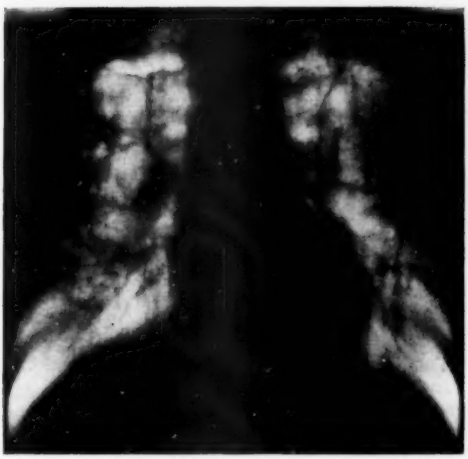

FIG. 2.—Gross fibrosis and avascular cavitation five years after bronchial gland enlargement which had been overlooked.

In 1953-54 there was an epidemic of erythema nodosum in adults in two counties of Northern Ireland and Dr. J. W. Winchester, the area radiologist, wrote to me that he had found 30 cases running the course of sarcoidosis. The region is very sparsely populated, with no large towns in it and no facilities for an extensive field survey. Dr. Winchester made what enquiries he could and writes that there were many more cases treated at home or untreated. He questioned the water supplies as a source of infection and for what it is worth he has found out that in the majority of cases the water supply was a well of the shallow type in the garden. Michael, in a recent survey of 300 cases in America, explains

the higher incidence in negroes, 22–1, not on a racial but on a geographical basis, most of them coming from the rural South and he suggests soil and water studies. There is clearly a need for an epidemiological survey in this country.

It is generally assumed that the asymptomatic cases do well but an occasional one deteriorates. Fig. 2 is that of a boy who had enlarged glands five years previously—these were overlooked and he has now gross fibrosis and avascular cavitation with dyspnœa. The need for continual observation of these cases is obvious.

The pulmonary changes usually appear after the glandular enlargement. In most cases the spread is slow over six to twelve months or even longer; exceptionally, the lungs are diffusely involved in a month or less. The pulmonary lesions as seen radiologically are of three distinct types. In the commonest the nodes are widely scattered but not clumped. They are of unequal size, some being only 1 mm. and others 3 or even 4 mm. They seem to favour the middle zones or rather the dorsal segments of the lower lobes but if antero-posterior views and tomographs are made numbers of them are found in other areas. Fig. 3 is type 1 which is often accompanied by type 2 when some interstitial change occurs and a coarse linear pattern appears along with the mottled nodules. This striation should not be interpreted as fibrosis or the precursor of fibrosis for it can disappear as completely as the other lesions. The third type is a true miliary disease with all the nodules equal in size and the whole of both lungs involved. Type 3 is indistinguishable from many other miliary diseases but I think that types 1 and 2 if accompanied by splaying of the hila are characteristic of sarcoid. It is very unusual for only one segment or one lobe to be involved and I have seen this only twice following glandular enlargement.

Occasionally, large round nodules like tuberculomata or metastases occur. These have an odd distribution which should arouse suspicion. Large lumpy deposits, similar to those in the liver and spleen, are very unusual in the lungs.

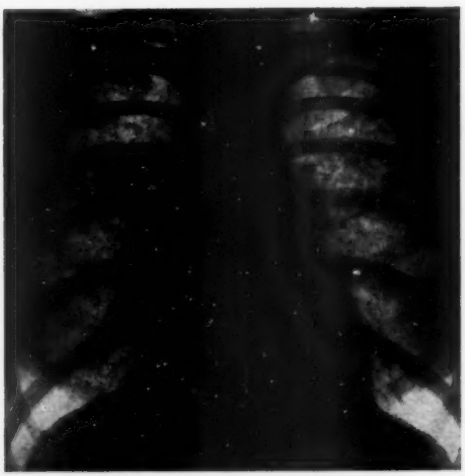

FIG. 3.—The common type of pulmonary sarcoidosis. Note the main distribution of the lesions in the middle zones (lower lobes) and the varying sizes of the nodules.

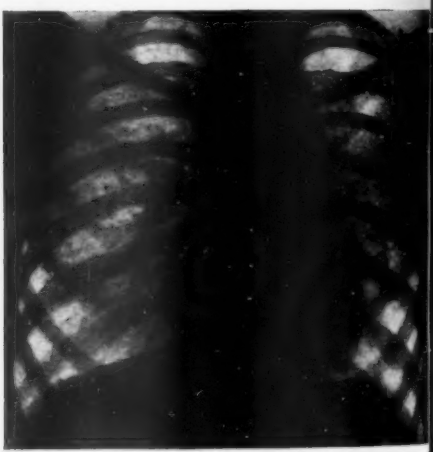

FIG. 4.—Sarcoidosis with nodular and interstitial changes. Eventual reversion to a normal picture.

If fibrosis develops, the extent to which it occurs cannot be estimated from the preceding changes. A most extensive lesion may leave patchy fibrosis limited only to a lobe or one or two separate segments. Basically, all forms of pulmonary fibrosis look alike with long fibrinous strands and traction on vessels and the mediastinal structures. Some get focal emphysema with a honeycomb lung and some develop large avascular cavities. There are two interesting features about sarcoid fibrosis: (1) There is never calcification in it which serves to distinguish it from tuberculous fibrosis, and (2) there is seldom, if ever, pleural fibrosis. Pleural fibrosis with a shaggy mediastinum and diaphragm is common to all the late pneumoconioses and many of the chronic pulmonary infections resulting in fibrosis but sarcoid seldom involves the serous membranes. Even in the acute fulminating fatal cases the serous membranes escape. The only case I have seen with pleural fibrosis was

in a patient who developed sarcoidosis after he had recovered from active pulmonary tuberculosis.

The bone changes in sarcoid of the phalanges are well known, with a widened trabecular pattern, cysts, expansion of the bone without periosteal reaction and even pathological fractures. It should be emphasized that at autopsy the phalanges have been found to be full of sarcoid with only minor changes in the trabeculation. Some put the incidence of bone lesions at 20% but I have only found it twice in just over 300 cases. It is said to be rare in other bones but on reviewing my cases I have found one in the outer end of the clavicle.

Lesions in other organs which can be radiologically investigated are rare. There are a small number recorded in the gastro-intestinal tract where a submucosal fibrosis with ulceration can simulate carcinoma and ulceration in the œsophagus and stomach and regional ileitis in the small bowel. These can only be suspected to have a sarcoid basis if the clinical findings are suspicious or if the X-ray signs of intrathoracic sarcoidosis are present.

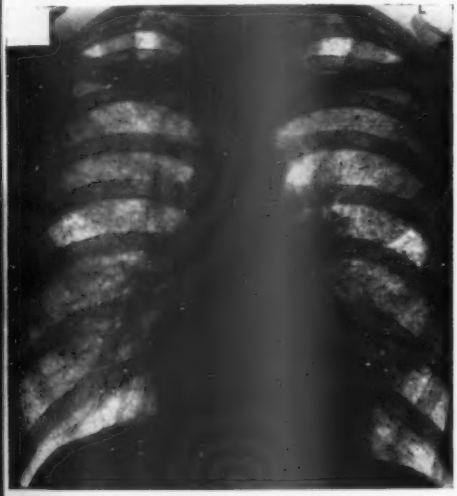

FIG. 5.—True miliary sarcoidosis.

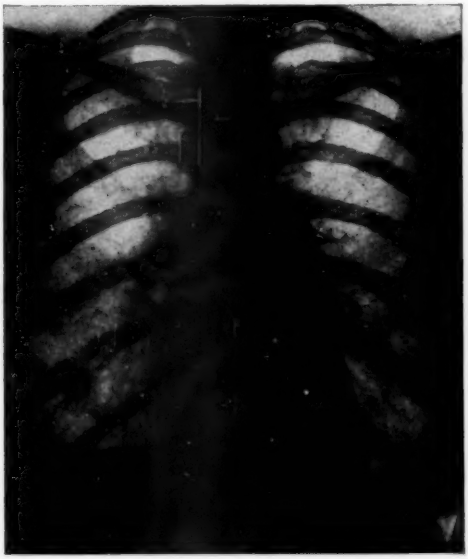

FIG. 6.—Round deposits in the right lower lobe in sarcoidosis. The glands enlarged later.

Involvement of the heart or cardiovascular system is rare but is of great importance since it is one of the immediate causes of death. There are quite a number of cases recorded in which large sarcoid deposits were found in the myocardium at autopsy. There is one recently recorded death with all the classical signs of cardiac ischæmia where autopsy showed myocardial sarcoidosis and fibrosis constricting the coronary arteries. I have seen other cases in young people with heart block and flutter who have had pulmonary manifestations of sarcoidosis. They have shown no radiological evidence of cardiac disease. I have, however, found one case in which the transverse diameter of the heart gradually enlarged up to 3 cm. and subsequently reverted to normal over a period of eighteen months. Cardiac involvement was never suspected in this patient.

There is also a steadily increasing number of cases developing malignant hypertension. The relationship is quite obscure since most of them have not been found to have renal sarcoidosis. Berger and Relman who have studied this aspect intensively think it is due to a disorder of calcium metabolism in sarcoidosis while Ricker and Clark in other cases have found a renal arteritis and periarteritis. In my series there are two cases. One, a boy of 19, was admitted to Westminster Hospital with iritis and a fever of 101° F. Two months later there were pulmonary lesions consistent with sarcoidosis. A diagnosis of sarcoidosis was established and for a brief period he recovered. There was a relapse followed by the rapid development of malignant hypertension, failure and death. Autopsy revealed sarcoid

lesions in glands and in the interventricular septum but none in the kidneys. The total duration of the illness was eighteen months. The second patient developed uveoparotitis five years ago. While this waxed and waned thoracic signs arose, first massive glandular enlargement which receded and was followed by miliary infiltration in both lungs. All these lesions have disappeared but malignant hypertension is now established and resistant to all methods of treatment. In both of these there was gradual insidious cardiac enlargement. A third case with all the clinical features of polyarteritis, fever, leucocytosis, eosinophilia, joint pains and muscular pains had the pulmonary X-ray signs of sarcoidosis and over three years made a complete clinical and radiological recovery on cortisone. Twenty-five years ago in the literature, this combination was described as a particularly fatal type of Hodgkin's disease.

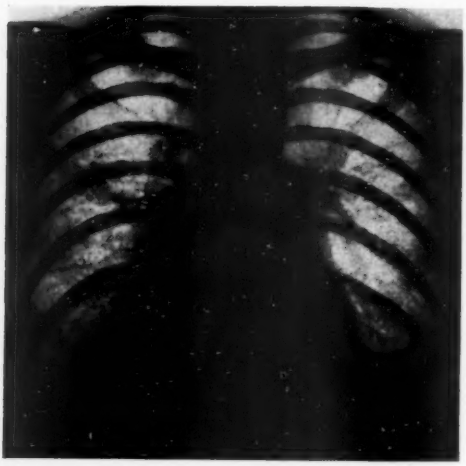

FIG. 7.—Gradual cardiac enlargement in sarcoidosis.

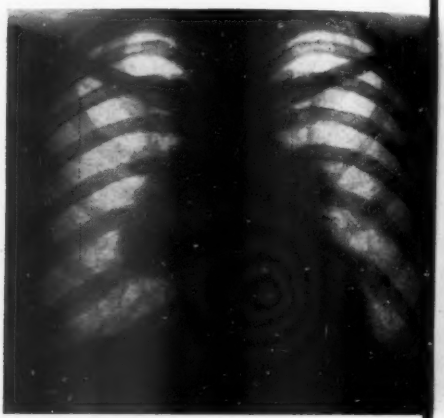

FIG. 8.—Sarcoidosis of the bronchial glands associated with a hydatid cyst.

There are many other bizarre clinical combinations. Brian Taylor and his colleagues have described carcinoma of the lung supervening on pulmonary sarcoid. I have seen one patient who had active pulmonary tuberculosis with a positive sputum, cured by chemotherapy; subsequently she developed asymptomatic pulmonary sarcoidosis and her Mantoux reaction became negative. Another girl, a nurse, who converted from Mantoux negative to positive following BCG inoculation, got systemic sarcoidosis twelve months later and reverted to Mantoux negative.

During the past twelve months the following three combinations have been seen in Westminster Hospital: sarcoid in association with mitral stenosis, sarcoid in association with ankylosing spondylitis and sarcoid in association with a hydatid cyst.

These combinations may be fortuitous or allergic but whatever the ætiology of the disease, it has a significant mortality and may be steadily on the increase.

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Mr. A. G. Cross: *Ocular Sarcoidosis*

Sarcoidosis, which is a granulomatous type of inflammation, may affect any tissue of the body and frequently it involves the eyeball and the ocular adnexa. The eye affection may be the first manifestation of the disease, and it is interesting to recall that the first description of sarcoidosis was written by Jonathan Hutchinson who was a surgeon on the Staff of Moorfields Eye Hospital.

The morbid histology of sarcoidosis is characteristic and its appearances in the eyeball differ in no way from those elsewhere in the body. One part of the eyeball may be affected or there may be generalized infiltration of the granulomatous tissue throughout the whole organ. The ocular adnexa may be affected in association with the disease of the eyeball.

Lesions in the Eyeball

(1) *Uveitis* is the most common ocular lesion of sarcoidosis. This may affect the iris and the ciliary body to give anterior uveitis (iridocyclitis), or the choroid to produce posterior uveitis (choroiditis). Some cases may show a general affection of the whole uveal tract known as panuveitis. The involvement of the uveal tract by sarcoidosis shows certain well-defined clinical characteristics. (*a*) *Anterior uveitis:* Characteristically this is a nodular iritis. Macroscopic nodules of granulation tissue are present in the iris in many cases, and are usually situated near the periphery. Sometimes the nodules may be smaller and they may not be visible to the naked eye, though they can be seen by microscopic examination of sections of the diseased iris tissue. The K.P. are typically very large, confluent, and they have a translucent ground-glass appearance. (*b*) *Posterior uveitis:* Nodular lesions are present in the choroid usually situated near to its periphery. The uveitis of sarcoidosis is frequently, but not invariably, bilateral and it may occur acutely with redness and pain of the eye, or as a more chronic condition when these symptoms are absent. It may lead to all the usual complications of uveitis, including secondary glaucoma and complicated cataract. The inflammation of the uveal tract may be accompanied by sarcoid infiltration of the parotid gland, and this is one cause of the uveo-parotid syndrome (Cross, 1953).

(2) *Conjunctivitis.*—Sarcoid follicles may be present in the conjunctival fornices, and in the bulbar conjunctiva. Crick, Hoyle, and Mather (1955) have developed the method of biopsy and microscopical examination of the conjunctiva in suspected cases of sarcoidosis, and it seems that this procedure may be useful in the routine examination of suspected but undiagnosed cases.

(3) *Sclera.*—Sarcoidosis may occur in the sclera, and it appears as a localized scleritis which may be accompanied by uveitis. Healing leaves weakened fibrous tissue and this, subsequently may lead to the formation of a staphyloma.

(4) *Cornea.*—The cornea may be involved by a spread of the pathological process from the sclera, and some patients who have suffered a severe uveitis may show the condition known as band degeneration of the cornea.

(5) *Perivasculitis retinæ.*—This condition of inflammation of the retina, particularly around the retinal vessels, which was originally described as Eales' disease, may be due to sarcoidosis. It shows no characteristic features, when due to this condition. It was, for many years, considered to be a tuberculous periphlebitis, but it appears that its ætiology is as varied as that of uveitis and that, in some cases, sarcoidosis may be the responsible agent. Perivasculitis retinæ usually manifests itself by recurrent vitreous hæmorrhage, and hæmorrhages and exudates are present in the periphery of the retina. Organization of the vitreous hæmorrhage may lead to retinitis proliferans and retinal separation. It may be accompanied by uveitis (Cross, 1955).

Lesions in the Ocular Adnexa

(1) *The eyelids.*—Sarcoid lesions may be present on any part of the skin of the body, and the eyelids may be affected. This lesion appears, in some cases, to be an isolated manifestation of the condition.

(2) *The orbit.*—Masses of sarcoid granulation tissue may be deposited in the orbit where they give the signs of an orbital tumour.

(3) *Lacrimal gland.*—Deposits of sarcoid tissue may be present in the lacrimal gland, when the secretion of tears may be reduced, and keratoconjunctivitis sicca may occur.

Diagnosis.—Ocular manifestations of sarcoidosis appear in two groups of patients. (1) *The first group*, having the eye condition as its primary lesion, appear in the Eye Hospitals and in the Ophthalmic Departments of General Hospitals. The ocular condition is diagnosed but its cause may be difficult to identify, in spite of the fact that some of the clinical manifestations of sarcoid are characteristic. Skin lesions may be removed for microscopic examination and enlarged lymphatic glands, when present, may be subjected

to biopsy. Routine X-ray examination of the lungs and, rarely, of the bones may yield confirmatory evidence that sarcoidosis exists, and a negative Mantoux reaction in an adult may be suggestive evidence. Most ophthalmologists do not undertake liver puncture. Serum protein estimation does not appear to be of great value. Some patients in this group may have their eye condition for months or even years before the development of a skin lesion or a lymphadenopathy allows the diagnosis to be made with some certainty. (2) *The second group* comprises patients with established sarcoidosis in whom a lesion appears in the eyes, and in whom it is reasonable to suppose, at least in the majority of patients, that sarcoidosis is the cause of the eye condition. Crick (1955) has reported that, in his series, ocular lesions were found in 33% of proved cases of sarcoidosis.

Treatment.—Eye lesions require general treatment as well as local treatment. Some of these cases have been treated during the past four years at the Eye Sanatorium at Swanley where, under the usual sanatorium regime, they have improved greatly. Local treatment depends upon the site of the lesion in the eyeball. Cortisone used as drops or by subconjunctival injection is very valuable in cases of anterior uveitis and scleritis. Some have cleared in a dramatic manner. Patients with posterior uveitis and with perivasculitis retinæ have improved as a result of a course of systemic cortisone. It is very striking that patients with ocular sarcoidosis settle much more effectively if diagnosed and fully treated at an early stage before a fibrosis has caused permanent changes in the tissues of the eye. Patients who have developed such complications as secondary glaucoma and cataract seem to be much more resistant to therapy. This is found also in other diseases of the eyes and of the rest of the body, but it is very marked in cases of ocular sarcoidosis.

Ætiology.—The cause of sarcoidosis and the mechanism of its development appear to be unknown. The relationship to tuberculosis appears definite, but it seems certain that this is not the only cause. The condition can occur at any age, but appears more common in early adult life and in later life. It occurs in all grades of severity from apparently isolated lesions to a generalized affection of the whole body.

The relationship between uveitis and sarcoidosis is of interest. The causes of uveitis are many and the mode of its causation, as of sarcoidosis, is uncertain. Some cases of uveitis, it is supposed, are the result of a sensitivity of the uveal tract to toxins produced elsewhere in the body—whether by infection of the teeth, tonsils, gut, lungs or any other organ. It is attractive to postulate that sarcoidosis develops by a similar mechanism, but that the sensitivity—instead of being restricted to the uveal tract—affects the many other tissues of the body.

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Section of Orthopædics

President—Sir REGINALD WATSON-JONES, M.Ch.Orth., F.R.C.S.

[*March* 10, 1956]

MEETING AT THE LONDON HOSPITAL

Osteochondritis of the Medial Sesamoid of the Great Toe

By C. G. ATTENBOROUGH, M.Chir., F.R.C.S.

THERE are numerous conditions which cause pain under the head of the first metatarsal. During a period of three years, three out of the many patients seen with this complaint at The London Hospital, appear to be examples of a condition which has received only scant attention in orthopædic literature.

CASE HISTORIES

Case I.—In October 1952, a male patient aged 20, a medical student, complained of pain in his right foot, under the head of the first metatarsal. There was local tenderness and an X-ray showed fragmentation of the medial sesamoid (Fig. 1). He was treated by protecting the tender area by a felt ring and his symptoms subsided within a few weeks.

In February 1955, the medical student returned, this time with pain in his opposite foot. The medial sesamoid was found to be fragmented and sclerotic. His right foot was painless, and an X-ray showed that many of the previously-noted fragmented areas now appeared to have coalesced, but the sesamoid was still flattened (Fig. 2).

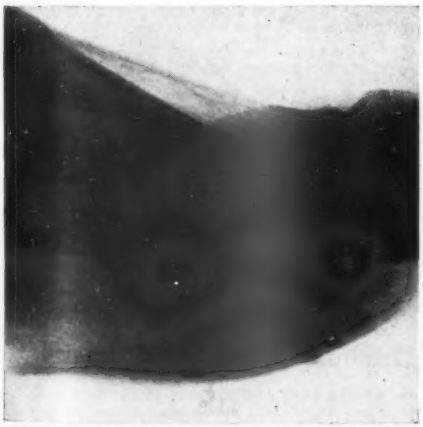

FIG. 1 (*Case I*).—Right foot 1952. Fragmentation of medial sesamoid.

FIG. 2. (*Case I*).—Right foot 1955. Coalescence of some of the previously-noted fragmented areas.

Case II.—In February 1953, a schoolboy of 15 complained of pain under the ball of his right foot. The pain had been present for several months, was noticed only on weight bearing, and there was no history of injury. He was tender under the medial sesamoid. An axial radiograph showed that the medial sesamoid in his right foot was slightly granular in appearance and a little flattened (Fig. 3). He was treated by a felt pad to take the weight off the tender area and his symptoms subsided over a period of two to three months.

Case III.—In summer, 1955, a schoolboy of 11½ years was seen with pain under the head of the first metatarsal of his right foot. The symptoms had been present for about three months. An X-ray showed quite definite fragmentation and a little distortion of the medial sesamoid.

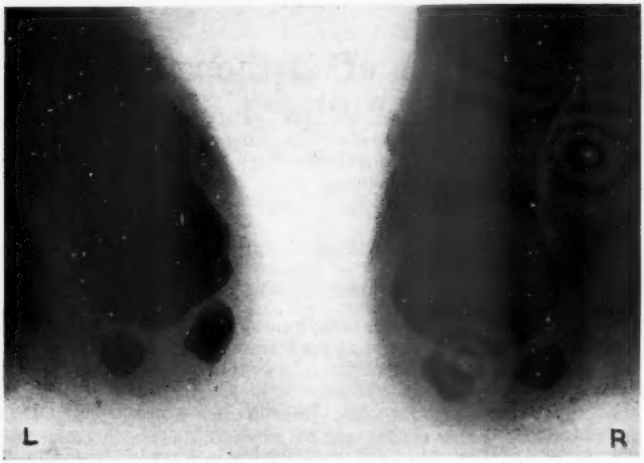

FIG. 3 (*Case II*).—Axial view of sesamoids showing slight flattening of right medial sesamoid which is granular in appearance.

DISCUSSION

Two patients with osteochondritis of the medial sesamoid of the great toe were reported by Renander in 1924. His patients were a schoolboy of 13 and a woman of 36. These two are mentioned by Brailsford (1953) but I have found no other reference to this condition.

It might be suggested that these 3 patients have congenital abnormalities of the medial sesamoid. A bipartite sesamoid is very well known. However, the radiographic appearances in these patients do show typical changes of osteochondritis in all stages. Firstly, the early fragmentation and flattening (Fig. 3). Then the development of sclerotic areas. Then sometimes the more marked fragmentation (Fig. 1), and finally (Fig. 2) the stage when the bony islands appear to fuse together as the re-ossification occurs, leaving some permanent flattening.

This condition may be more widely recognized than would appear from a study of the literature.

In the discussion it was agreed that this was a definite clinical entity and should be treated conservatively with simple protective pads in the shoes.

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Treatment of Crush Injuries of the Hand or Foot by Early Irradiation

By ADRIAN E. FLATT, M.D., F.R.C.S.

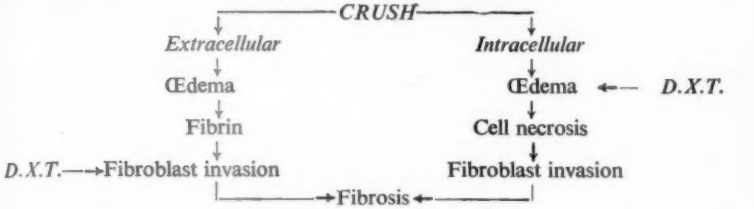
THE accepted regime of treatment for these injuries is elevation, pressure dressings and early controlled activity. These desiderata are not always compatible with the treatment of accompanying lesions such as skin loss and fractures.

It seems that this standard treatment is not really related to the natural pathological history of the condition. There is both intra- and extra-cellular œdema. No matter by what means the pressure is applied the inevitable sequel is a swollen œdematous part infiltrated with fluid rich in protein. This precipitates fibrin between all the moving parts, and even between the cells of each tissue. The whole becomes organized with ingrowth of blood vessels and connective tissue until there results a firm congealed "frozen" hand or foot.

It is felt that radiotherapy could be of use in three phases of the pathological process:

(1) by increasing the permeability of the cell membrane it allows the intracellular œdema to drain out;

(2) by inhibiting the formation of young fibroblasts it decreases the fibrous organization of the damaged area;
(3) probably by enzyme inactivation the yield of fibrin is reduced.



Up to April 1956, 46 cases have been treated and 15 have been reviewed after being discharged from treatment.

All the injuries were of a relatively minor character and involved either a hand or foot.

The irradiation dose varied between 100 and 300 r, the majority of cases receiving 150 r. Two patients remained at work throughout treatment; one patient with compound fractures of all the metatarsals in one foot was off work for 71 days and the average working time lost for the series of 15 was 17 days.

All 46 cases so far treated have generally shown equally encouraging results.

The order of dosage of X-ray is such that it is well below the level which would affect the normal process of healing. We have treated cases with sutures in skin wounds, with split skin grafts *in situ* and with fractures of the phalanges, metacarpal or metatarsal shafts. In no case has the treatment had a detrimental effect on healing. There is no theoretical objection to treating cases which have metal pins transfixing fractures or in which an abdominal flap has been used to replace skin loss; though we have not as yet had occasion to treat such cases.

An unbiased scientific assessment of the results of treatment of these cases is naturally impossible and it can only be said that up to date a very definite clinical impression has been formed that these cases get relief from symptoms and have returned to work more quickly than similar cases treated without D.X.T.

Dr. Walter Shanks: I had never treated cases of crush injuries by irradiation before but it is a commonplace that prior to the introduction of antibiotics and indeed even to-day the treatment of choice for the carbuncle is a small dose of X-rays, which will relieve the pain within the first twenty-four hours, and the carbuncle itself subsides quite quickly. In the past the effect of X-rays on cells has been considered mainly as an effect on dividing cells, and on the histological changes on cell nuclei; but they have an effect not only on cell nuclei but on the intracellular enzymes and fluids and upon the cell membrane. It has been known for many years that even small doses of X-rays change the permeability of cell membranes. That can be demonstrated easily by injecting lamp black or any sort of dye which normally does not permeate into the cell and after a small dose of X-rays the lamp black or the dye will be seen in the intracellular fluid.

Therefore when Mr. Flatt asked whether I thought X-rays could reduce the incidence of the "frozen" hand following a crush injury, it seemed to me that they could be expected to do so.

X-rays in small doses assist the resolution of inflammatory swellings; all dividing round cells are extremely radiosensitive; the change from fibrinogen to fibrin, and the proliferation of fibroblasts are also inhibited. The yield of fibrin, fibroblastic proliferation, and extracellular fluid might therefore be expected to be reduced following small doses of X-rays.

For these reasons I thought there was a prima facie case for using small doses of X-rays in these cases, and they have responded well. The dose which I have used is a very small one, 50 r given on alternate days. In some of the cases I used more than that, 100 r, but after the first case it was quite obvious that a large dose of that order was not required. Most of the cases have had a dose of 150 r in a total time of five days.

It might be thought that for a benign condition of this kind it is unfortunate to apply ionizing radiation of any kind, but I think it is perfectly safe to give a dose of this order, a dose of 40 or 50 r to the skin might well be given in the course of a diagnostic X-ray examination and I do not think that a dose of this order is likely to have a neoplastic effect on the skin

Reducibility of Slipped Femoral Capital Epiphyses

By O. J. VAUGHAN-JACKSON, B.M., B.Ch.(Oxon.), F.R.C.S.

To my mind there is a wrong emphasis in our teaching on the management of slipped femoral capital epiphyses. We over-emphasize the evils of *manipulation* when what we really fear are the dangers of *force*.

In cases of recent slipping it is generally agreed that in minor displacements we accept the position and insert a trifin nail at once (or adopt such other methods of immobilization as we prefer). In major displacements it is deemed most unwise to correct by *forcible* manipulation, it being regarded as unnecessary in recent slips and dangerous in older displacements. On these grounds major recent displacements are corrected by traction followed by nail (or other) immobilization. Major old displacements are corrected by cervical osteotomy.

I entirely agree about the danger of *forcible* manipulation—the fear is that it will stretch or tear capsular vessels and cause avascular necrosis of the epiphysis. It is argued that if there has been an acute slip the manipulation will of course succeed, but simple traction would have done it without risk. In older slips, of say several months' duration, the danger is, it is said, inescapable as well as obvious. It all depends on what in fact is an acute slip and what is a gradual one, and on what is meant by "forcible" and what by "manipulation". My cases show that with either *no* acute incident in the history, or with no recent acute incident, it is quite erroneous to suppose that slips up to seven months old are *necessarily* irreducible without force.

My interest in the possibility of safe gentle reposition of the epiphysis began with a case before the war which had a history of several months and nothing to make me suspect an acute slip which, quite inadvertently, I reduced completely from a gross slip by allowing the hip to roll, under the limb's weight only, into internal rotation. After the war my interest was reawakened by my complete failure ever to obtain the slightest improvement by traction. What is more—despite what is written—I have never yet seen anyone else get anything but the slightest alteration in the position of the slipped epiphysis by traction. I suggest that where traction succeeds it is because it is also traction *in internal rotation*.

Remembering my inadvertent success I have made it a practice in every case of unhealed slipped epiphysis *no matter how old* to try the effect—with the patient anæsthetized—of allowing the hip to fall with the utmost gentleness, under the weight of the limb only, into internal rotation in the semiflexed position. (That may be a manipulation but it is most certainly not forcible.) The hip is then gently extended still in internal rotation and X-rayed. The results are often gratifying. Over and over again I have been told by a perfectly competent senior assistant that "Traction has failed—I think we can pin it as it is" or, "I've put the case down for a cervical osteotomy"—yet this simple manœuvre has been all that was necessary to obtain a very gratifying reduction. Such a case is shown in Fig. 1.

Tables I, II and III refer to nineteen hips and are largely self-explanatory. Table I is an analysis of nine hips in which there was no acute incident in the history. Note the average duration of history is seven and a half weeks. All were subjected to the manipulation described. It failed completely in 2, but achieved some success from slight to complete in all the remaining 7.

TABLE I.—RECENT SLIPPED EPIPHYSIS WITH SYMPTOMS

(*No Acute Incident in History*)

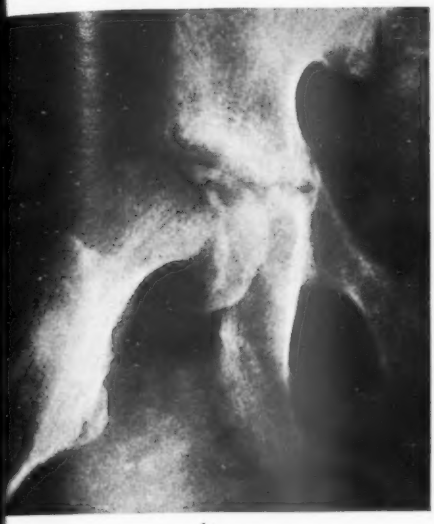
7 hips	Duration of symptoms	Displacement
4 male	Maximum 4 months	Slight 1
3 female	Minimum 2 weeks	Moderate 2
	Average 7½ weeks	Gross 4

ALL were manipulated.

RESULTS

Before	After	Follow-up
	(1) Anatomical	(2) Function
Slight	Perfect	Normal and symptom free at 5/12
Moderate	Good	Normal and symptom free at 6/12
Moderate	Fair	Normal and symptom free at 21/12
Gross	Improved (? degree)	Arthrodesed, fair function only
Gross	Good	Not known
Gross	Good	Avascular necrosis (epiphysis displaced by pin)
Gross	Perfect	Normal and symptom free at 6/52

In 2 *hips*, one male and one female, duration six weeks, six months, manipulation failed.



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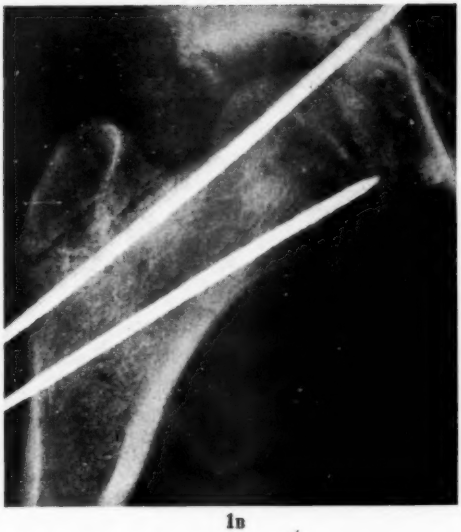

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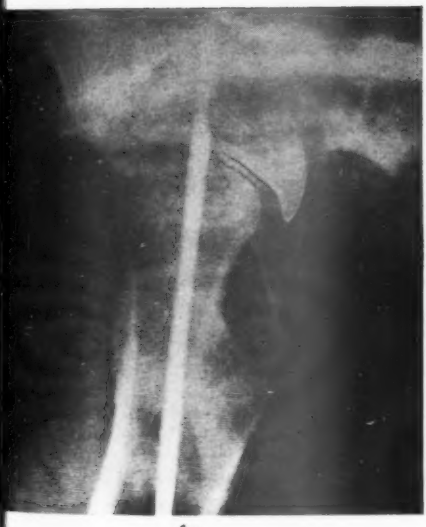

1C

FIG. 1.—A, Lateral view showing slip. B, Antero-posterior view showing reduction after manipulation. C, Lateral view showing reduction after manipulation. This case had a history extending back over three months and no acute incident in the history.

In Table II, 5 hips with acute incidents in the history responded in the manner one might expect but in three of them with long histories, no mention of an acute incident was made until after traction had failed, and the case was being considered for operation. Moreover in only 2 of the 5 cases were the acute incidents recent.

Table III summarizes the series. In 5 cases the manipulation was not attempted. In the 2 cases which developed avascular necrosis of the epiphysis there were obvious special reasons why they might do so quite apart from the manipulation. In one the nail displaced the epiphysis after satisfactory reduction. In the other, an extreme Batchelor position was adopted over several days while a suitable nail was obtained, the delay being due to the post-war shortage of stainless steel.

TABLE II.—RECENT SLIPPED EPIPHYSIS WITH SYMPTOMS

(*Acute Incident in History*)

5 hips	Duration of symptoms	Displacement
3 male	Maximum 7 months	Moderate 2
2 female	Minimum 10 days	Gross 3
	Average 9 weeks	

Traction attempted in 3. *Failed in* 3.

ALL were manipulated

RESULTS

Before	After	Follow-up
	(1) Anatomical	(2) Function
Moderate*	Good	Normal and symptom free at 21/12
Moderate*	Perfect	Not known
Gross	Perfect	†Normal and sympton free at 47/12
Gross*	Perfect	Normal and symptom free at 14/12
Gross	Perfect	Normal and symptom free at 31/12

NOTE.—*In these cases the history of an acute incident was obtained *after* traction had failed.
†Developed avascular necrosis—probably due to primary injury or Batchelor position.

In 5 *hips* *traction failed or was not attempted.*
No manipulation was attempted.
Pinning was carried out in 3.
Pinning after cervical osteotomy in 2.

A long history is not to be taken as meaning that the opportunity for gentle reduction is necessarily past. I am myself convinced that it is internal rotation which reduces these displacements, not mere traction, and, therefore, unless we *test* each hip by this manipulation of surpassing gentleness we are going to miss reducible hips. We will nail them in the position of deformity or operate on them unnecessarily (I know of one case where at open reduction the epiphysis was found quite loose). Alternatively we will drag on capsular vessels by long-continued traction when five seconds testing of the hip in this way would reveal the reducibility and secure reduction.

TABLE III.—SUMMARY

In Series of 19 *Hips*

Manipulation improved or corrected deformity in ..	12
Manipulation failed in	2
Manipulation was not attempted in	5
Traction attempted in 3 and failed in	3

Osteoarthritis of the Hip-joint

Many cases demonstrating the results of operative treatment of osteoarthritis of the hip-joint were shown.

Mr. W. Alexander Law showed 7 cases of arthroplasty of the hip, 6 of which were more than five years after operation, and 2 of which were bilateral cases. Patients demonstrated their ease of sitting, the absence of a Trendelenburg lurch in their gait, ability to climb stairs and their freedom from pain. They were all cases of osteoarthritis, with one exception, a young patient of 26, who was suffering from ankylosing spondylitis, and who had both hips treated at one operation.

Sir Reginald Watson-Jones, President of the Section, emphasized the benefit of arthrodesis in unilateral osteoarthritis which, if correctly performed with proper after-treatment, permitted almost unlimited physical activity and recreation, including walking for ten or twenty miles without need to use a walking stick, climbing mountans and ski-ing, comfortable sitting, and no pain in the hip or in the low-back.

There was a full discussion on the papers and on the 29 cases shown at the afternoon session.

Section of Dermatology

President—LOUIS FORMAN, M.D., F.R.C.P.

[*February* 16, 1956]

Chronic Granuloma of the Gum with Swelling of the Lip in a Patient handling Sodium Silicate Solution.—LOUIS FORMAN, M.D., F.R.C.P., and C. W. SHUTTLEWORTH, M.R.C.S., L.R.C.P., F.D.S. R.C.S.

Miss D. T., aged 56.

This case was seen originally by Dr. A. G. C. Cox of St. Olave's Hospital to whom we are indebted for permission to show her.

She uses an alkaline solution of sodium silicate to coat cartons of biscuits. In June 1953 her hands were in contact with this solution which was spilled on the floor. The hands began to itch and she developed a habit of rubbing the right hand on the lips and teeth of the right upper jaw. The upper lip became swollen and has remained so. There has been direct contact with the silicate solution since, although she wears a protective cotton glove, which itself becomes stiff with dried silicate.

On examination in 1955 she showed an excoriated and lichenified dermatitis of the wrists and fingers. The right upper gingival mucous membrane was reddened and swollen and retracted from the teeth (Fig. 1). There was considerable deposition of tartar around the teeth. *Biopsy of gum* in 1955 showed a chronic infiltration of lymphocytes, plasma cells and fibroblasts beneath the epithelium, with foreign body giant cells in relation to small areas of calcification. *Biopsy of the lip:* Capillary dilatation and a small node of histiocytes with foamy protoplasm. W.R. negative, blood count and differential normal. E.S.R. 29 mm. in one hour (Westergren). Smears and cultures for yeasts, actinomyces and tubercle bacilli were all negative.

Dr. B. Cooke (Dental Department, Guy's Hospital) noted bi-refringent particles in the section from the gum. The section was heated to 500° C. for an hour with concentrated HCl and after the treatment similar particles were seen. The particles seen after treatment, however, may have been derived from the air or walls of the furnace, for they were not identified with the original bi-refringent particles seen in the section.

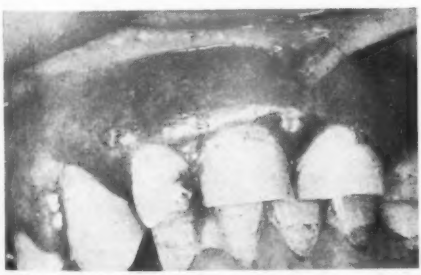

FIG. 1.—Swelling, redness and retraction of the gingival mucous membrane of the right upper jaw.

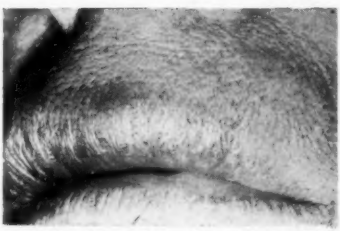

FIG. 2.—Chronic swelling of the right upper lip.

Comment.—The appearance of the localized gingivitis is not unusual either as a result of tartar or chronic periodontal infection. The calcium deposit seen in the section may be tartar, calcified epithelial fragments, or calcium deposited around solid sodium silicate particles. The swelling of the lip (Fig. 2), which varies in intensity in this patient, might be due to a sensitivity to sodium silicate, or to spread of silicate along the lymphatics from the gum to the lip, or a recurrent lymphangitis. Silica deposited in tissues can give rise to a chronic granulomatous reaction many years later (average fifteen years). It may spread to the regional lymphatic glands (Shattock, 1917). It could be introduced into the mucous membrane in the dentist's polishing paste. In this instance the particles would be of sodium silicate more soluble than silica (SiO_2) and capable of exciting an immediate rather

than a delayed reaction. The solution of sodium silicate used was so strongly alkaline as to be unsuitable for patch tests. When neutralized a semisolid gel was formed of silicic acid which gave a negative patch test on the skin of this patient.

REFERENCE.—SHATTOCK, S. G. (1917) *Proc. R. Soc. Med.*, **10**, Sect. Path. 6.

The President: Epstein (1955) recorded a case of silica granuloma affecting the cheek which was caused by glass forced into the skin as a result of a motor accident 10 years previously.

The granuloma was resolved by six weeks of cortisone commencing with 200 mg. and reducing to 75 mg. a day.

REFERENCE.—EPSTEIN, E. (1955) *Arch. Derm. Syph., Chicago*, **71**, 24.

Chronic Granuloma of Alveolar Mucous Membranes, and of the Lip and Chin, ? Foreign Body Granuloma, ? Lupus Vulgaris.—LOUIS FORMAN, M.D., F.R.C.P., and W. G. CROSS, M.S., B.D.S., L.D.S. R.C.S.

Mrs. E. H., aged 47. At age 13 fell and broke two front teeth, cut lower lip. *Erythema nodosum* (1936) on legs. *Appendicectomy* 1937; appendix showed a thickened wall with considerable fibrosis and giant cell systems—examined by Mr. I. R. H. Kramer of the Eastman Dental Hospital for bi-refringent particles with negative results. Calcified glands present in the sacro-iliac region. 1938: *Hæmorrhages* from the bowel with bouts of diarrhœa. The gums were swollen and tender from this time (Fig 1). Hæmorrhages continued until 1948 when *multiple polypi* were demonstrated in the transverse and descending colon and the colon was removed. *The gums remained* swollen and tender and in 1949, a day after a tooth was filled, the right side of the lower lip became swollen and painful. The upper lip has also shown some swelling: Both lips, particularly the right side of the lower lip, have remained tumid. The adjacent skin of the lower lip became cyanotic and infiltrated. The infiltration has involved a wedge of skin down to the chin, but has resolved in the area immediately below the red of the lip and is now best seen on the chin (Fig. 2). Gingivectomy was performed by Mr. Cross, with considerable improvement of the gum swelling, and limited gingivectomies have been required since, when interdental swelling of mucous membrane has recurred.

The epithelium around incisors and canines, upper and lower, is seen to be thickened and reddened. There have been three episodes of swelling of the lip with malaise.

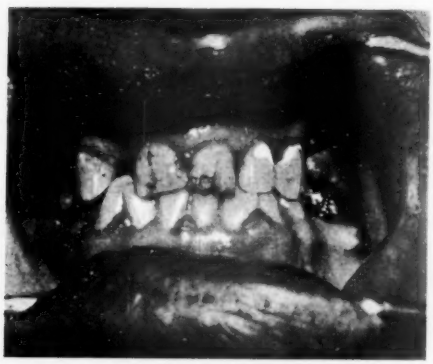

FIG. 1.—Chronic granulomatous gingivitis.

FIG. 2.—Chronic granuloma of the skin of the chin and lower lip.

Investigations.—X-ray of the chest—negative. Tuberculin 1/100 strongly positive. W.R. negative. Blood count normal. Blood proteins normal. Agglutinations to *Bracella melitensis* and *Brucella abortus* negative.

Histology (I. R. H. Kramer).—Gingival specimens removed in 1951 and 1954 have shown an identical histology. "Through the corium there is a very dense, almost tumour-like, infiltration with inflammatory cells amongst which plasma cells predominate. In various parts of the papillary layer numerous tubercle-like structures, sometimes consisting of aggregations of pale endothelioid cells and sometimes containing two or three Langhans type giant cells. As in previous specimens there is a predisposition to the formation of

epithelial masses detached from surface epithelium; it is not possible to be dogmatic about the relationship between these detached epithelial masses and the tubercle-like structures".

Biopsy of the lip and chin, in 1951 and 1955 "showed sub-epithelial giant cells follicles consistent with tuberculosis. No acid-fast bacilli were seen. No refractile particles suggestive of silica were seen."

Treatment.—Calciferol given for three weeks only and was not tolerated. Streptomycin 1 gram a day had to be discontinued because of swelling of the lips and malaise, after three days. Isoniazid given in 1954, 200–300 mg. a day for twelve weeks without definite resolution of the infiltrate of the lower lip and chin.

Two courses of penicillin, intramuscularly, daily for seven days with some temporary improvement. Two injections of hydrocortisone into the infiltrated skin on the chin did not produce any resolution.

Comment.—We have shown this patient because of the somewhat unusual collection of physical signs—and the difficulty in integrating them. This patient was for a time under the care of the late Dr. H. W. Barber who considered her as a case of recurrent infective, ? streptococcal lymphangitis and not of lupus vulgaris. The significant features are the history of tubercles in the appendix, the polypi, the chronic gingivitis and the œdema and granuloma of the lip and chin. This puzzle would encourage somewhat wide associations between morphology and ætiology. The alternative would be to divide the manifestations in this patient into separate ætiologies—thus polypi are common, they may be familial and presumably appear as a developmental epithelial adenomatous hypertrophy; the appendicular inflammation with the calcified abdominal glands might well be accepted as tuberculous, and this correlated with the chronic granuloma of the lip, itself considered by the pathologist to be tuberculous. However, the chronic gingivitis would be difficult to accept as tuberculous. The affected alveolar or periodontal epithelium is smooth, limited, and does not suggest the progression of lupus vulgaris, present ten years, without extension.

This type of chronic gingivitis has been described by Kramer (1951) as caused by a silicious granuloma. He found anisotropic crystals in three specimens out of a total of 66 patients with simple chronic gingivitis.

There would therefore need to be three different pathologies: the chronic granuloma of the gingival mucosa, either chronic infective or possibly due to silica or another foreign body (tartar, fragment or bristles, &c.); lupus vulgaris of the lip in a patient with previous tuberculous disease of the appendix; and polyposis of the colon of unknown origin.

The lip infiltration did not make a definite improvement with isoniazid 200 to 300 mg. a day over twelve weeks and although this dose is by no means the maximum one, in fact rather near the minimum of 3 mg. per kg., yet the result was not as expected, if the granuloma were tuberculous.

My suggestions for a single pathology are merely tentative, as it has no definite support in the laboratory findings.

The first suggestion: that a silicious granuloma of the gingivæ is present with the well-known liability of this tissue to support and to be subject to tuberculous infection.

The acute œdema of the lips following operative procedure might be due to secondary infection and lymphangitis which would encourage the spread of tuberculous infection.

The second suggestion: to consider the whole picture as due to silica. To do so would mean special pleading. Thus silica, hydrated in the tissue to form colloidal silicic acid, has been shown to be absorbed along lymphatics (as can crystals of silica), and might provoke the granuloma of the lip. No foreign body particles were seen in this case, but particles may be small in size, 1 μ, and not easily demonstrated. Silica may be present in colloidal state, or even in solution of sodium silicate. Thus the demonstration of silica may be difficult. There is also the factor of individual susceptibility or sensitisation to silica.

Refvem (1948) has reported that in 2 cases of 34 examined, bi-refringent particles were present in the granuloma of regional ileitis. A limited reaction to silica particles might therefore be expected in the appendix with the formation of tubercles. He also showed particles of silica in polypi of the anal and rectal mucosa. The source of silica might be talc, dust, dentist's grinding paste, vegetables and bran.

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Mr. W. G. Cross: I saw this patient first in 1949 when she attended complaining of soreness of the gums and also of the swollen lip. As far as the silica possibility is concerned, I think one might expect to find the lesions a little more widespread. I feel a little doubtful about the possibility of producing a silica reaction from polishing pastes.

In Kramer's series of cases where gingival biopsies were examined, the clinical history did not give any evidence of granulomatous reactions or appearance (Kramer, 1951, *Brit. dent. J.*, **91**, 309).

Dr. P. J. Hare: Why do you exclude sarcoidosis?

The President: The histology of the granuloma in my view was not that of sarcoidosis. Further, the Mantoux was strongly positive. Subsequently she had a further course of isoniazid for seven weeks, up to 400 mg. a day, without definite change.

Dr. G. B. Dowling: Am I right in supposing that you have excluded from your mind the possibility that tuberculosis may be the cause of this granuloma? It seemed to me that isoniazid had perhaps not been given for a long enough period as a therapeutic test to exclude that cause.

The President: In my experience, and according to the published reports, the dose of isoniazid given should have led to an improvement in a tuberculous granuloma of the gum and lip.

Dr. Brian Russell: I have a patient with irregular nodulation and elephantiasis of the lips, chin and malar region. Nine years ago at the age of 34 she was bitten by a puppy on the lower lip, and nine months later developed a red area which became nodular. One year later a papillomatous lesion developed on the right side of the tongue. It was not excised until three years later and proved to be tuberculosis in the submucosa. Subsequent biopsy from the chin was also typical of tuberculosis. I think she has lupus vulgaris complicated by streptococcal lymphangitis.

After two months' treatment with isoniazid 400 mg. a day she is experiencing subjective relief but there is no objective improvement. However, the prognosis remains fair because I have seen lupus vulgaris clear up after eight and a half months' treatment with isoniazid in an arm grossly swollen from post-mastectomy lymphœdema. Prognosis regarding lymphœdema in these cases is poor.

I think Dr. Forman's patient is also probably suffering from a tuberculous granuloma secondarily infected by streptococci.

Lichen Myxœdematosus.—ARTHUR ROOK, M.D., and J. L. MOFFATT, M.B.

Mr. F. L., aged 44, butcher. *History.*—First seen June 1955, when he complained that for six months the tips of the fingers had been sore and tender. Gradually the tenderness extended to the palms. At about the same time he began to feel the cold excessively. About one month before he was seen he developed recurrent swelling of the hands. This was always present on waking in the morning but soon subsided; two or three further attacks of swelling of short duration might occur during the course of the day. Over about the same period, he had noticed redness of the hands, varying in intensity but not in direct relation to the swelling. For a few weeks he had noticed small white spots, mainly on the reddened areas. He complained that for several weeks the grip of both hands had been weak, the right hand being the more severely affected. Since June 1955 he has attended on frequent occasions and the gradual extension of the redness to the upper arms and to the forehead, face and neck, buttocks and legs has been observed. He has no dysphagia, but recently has noticed difficulty in inserting his denture. He is a man of moderate and regular habits; he feels perfectly fit and makes no complaints other than the weakness of the grip.

His health in the past has always been good. He served in the Army from 1940–1945 and has been employed as a butcher since he left school.

On examination (9.6.55).—There was diffuse erythema of the backs of both hands and a more patchy erythema on the forearms, involving particularly the extensor surfaces; on many of the patches of erythema were numerous small white papules. There was slight infiltration of the skin of the fingers which did not restrict their movements. The palms were tender and it was difficult to decide whether there was any true muscular weakness or whether the tenderness accounted for the lack of strength in his grip.

On admission to Addenbrooke's Hospital (2.7.55).—Definite infiltration extended from the fingers to the wrists. The erythema of the hands and forearms was unchanged but there were new sharply outlined patches of erythema of the forehead and neck and there was infiltration over the glabella which produced a localized increase in the furrowing of the skin. The ears were red and possibly thickened (Fig. 2). There were large numbers of discrete pinhead papules on the hands, wrists and forearms and shins and the backs of the feet.

On examination (24.11.55).—The infiltration of the skin had extended to the forearms and had become more marked on the fingers. Dorsiflexion of the hands emphasized the infiltration of the skin which was thrown into deep transverse furrows (Fig. 1). There were numerous white papules, two or three millimetres in diameter, on the backs of the hands and on the forearms and arms, mainly on the extensor surfaces. The papules were slightly larger and more conspicuous than when the patient was first examined. The face and arms were red and infiltrated and there were numerous small papules on the chin. The mouth was small and could not be opened widely. The oral mucous membrane appeared normal. Some diffuse infiltration and redness were present on the buttocks and thighs where there were many dull red papules (Fig. 3). The lower legs were relatively little involved but

the changes on the ankles and feet were well marked and were similar to these on the hands.

Complete physical examination on three occasions has disclosed no abnormalities of heart, lungs or central nervous system. The grip of both hands is slightly reduced, but there is no definite evidence of muscular weakness.

Investigations.—Full blood count and E.S.R. (4.7.55, 5.7.55): within normal limits. Serum proteins (7.7.55): 8·1g./100 ml. The electrophoretic pattern was normal, but there was an increase in gamma globulin. Urinary creatine (5.7.55): 0·4 g./day. Urinary creatinine 1·2 g./day. Urine (6.7.55): Slight albuminuria.

Liver function tests (13.7.55): Serum alkaline phosphatase 3–5 Bodansky units. Thymol flocculation nil. Thymol turbidity 5 units (normal range—up to 4 units). Plasma cholesterol (24.1.56): 182 mg./100 ml. X-ray of chest and hands and a barium swallow revealed no abnormality.

Biopsy reports (Dr. A. M. Barrett).—12.7.55: "A piece of skin in which the corium is abnormal: the superficial half or more is different from the more normal deeper part and the abnormal part has abundant conspicuous connective tissue nuclei separated by coarse pale-staining collagen fibres. Ill-defined foci stain more deeply than the rest, and staining with toluidine blue and mucicarmine shows that metachromatic mucoid material is present in these foci. The mucoid material does not stain metachromatically with methyl violet."

"A section of skin in which the upper half of the corium is abnormal, containing more or less confluent large rounded areas of interstitial infiltration with a metachromatic substance which in its staining properties more closely resembles mucin than amyloid. It stains metachromatically with toluidine blue, is pink with mucicarmine, gives a positive reaction with the periodic acid-Schiff technique, and stains deeply but not metachromatically (or only slightly so) with methyl violet. The areas of infiltration tend to surround pilo-sebaceous follicles."

Comment.—When we first saw this patient the diffuse erythema and recurrent swelling of the face and hands and apparent muscular weakness were the most obvious features. The papular eruption was inconspicuous and variable. We felt that this was a condition we had not previously encountered; we hesitatingly considered dermatomyositis or scleroderma as possible diagnoses. The first biopsy showed only some œdema of the collagen and left us still in doubt. We are grateful to Dr. George Wells for suggesting the diagnosis of lichen myxœdematosus. The second biopsy taken at a stage when the infiltration of the skin had become quite extensive and the papular eruption was fully developed confirmed this diagnosis.

Montgomery and Underwood (1953) in their comprehensive article established lichen myxœdematosus as a definite entity and differentiated it clearly from other mucinoses with which it has been confused and to some of which the term lichen myxœdematosus

FIG. 1.—Dorsiflexed hand showing papules and transverse furrowing.

FIG. 2.—Papules, erythema and diffuse infiltration of the pinna.

FIG. 3.—Extensive eruption of firm dome-shaped papules on the buttock and thigh.

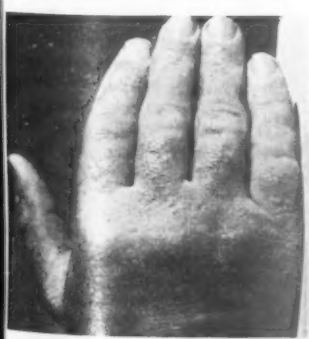

FIG. 1.

FIG. 2.

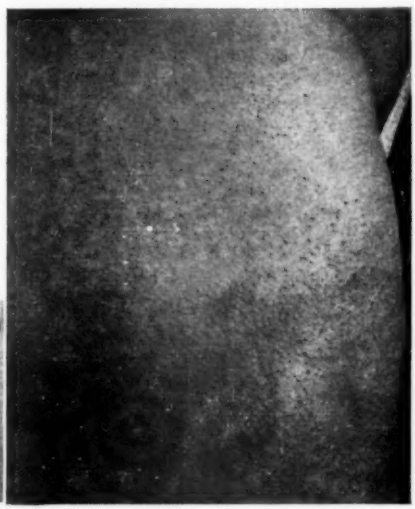

FIG. 3.

has sometimes been applied. It is certainly uncommon, although some cases have been reported under other diagnoses, particularly as atypical forms of scleroderma. The rarity of the condition perhaps justifies a brief summary of its essential features. Men have been affected slightly more often than women and the age of onset has ranged from 24 to 71, but has most commonly been between 40 and 60. The mode of onset is variable, but in the majority of cases the skin lesions have been the presenting manifestation. The most typical lesion is a pinhead lichenoid papule, large numbers of which may be present on the limbs and trunk and on the face, including the ears. In some cases large plaque-like lesions have also been present. The diffuse infiltration of the skin gives it a rubbery consistency and movements of the hands and fingers, and opening of the mouth may become restricted. The infiltration of the face may result in deep furrowing of the forehead and a lack of facial mobility, which combine to provide a rather characteristic worried appearance. The exaggerated creasing of affected skin overlying a joint is illustrated in Gottron's paper (1954). In some cases the mucous membrane of the mouth may be infiltrated. The tenderness which is so striking a feature in our patient may be the cause of apparent muscular weakness, as there is at present no evidence that systemic lesions occur in this disease. However, it seems probable that they will eventually prove to be present in extensive cases. The condition is progressive but may run a prolonged course; no effective treatment is known and there is apparently no response to the steroids (Donald *et al.*, 1953). The characteristic histological change is the presence of mucin in the upper dermis, often in the form of circumscribed deposits. The collagenous homogeneization of scleroderma is not present. The pathogenesis is unknown. Montgomery and Underwood (1953) suggest that there may be a disturbance of the balance of hyaluronidase.

In differential diagnosis the nodular and papular forms of scleroderma are most likely to cause confusion. Although some cases reported as nodular scleroderma were certainly examples of lichen myxœdematosus, the two conditions are not identical. The clinical differences and the strikingly different histological changes are clearly demonstrated by contrasting the present case with the example of nodular scleroderma presented to this Section by Seville (1951).

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Granulomatous Cheilitis.—ARTHUR ROOK, M.D., and J. L. MOFFATT, M.B.

Mr. W. E., aged 37, publican.

History.—His health has always been excellent. In August 1954 he developed a swelling of the lower lip. It varied in severity and was usually most marked in the early mornings and often subsided completely during the course of the day. There was some scaling of the lip which felt dry and slightly irritable. The swelling gradually increased over a period of six to eight months, the remissions becoming less frequent and less complete. During the past year the degree of swelling has remained constant. No other symptoms.

On examination (October 1954): Slight œdema of the lower lip but no induration. There was fine scaling of the vermilion border. He was re-examined at frequent intervals and by May 1955 the lower lip was considerably enlarged and partially everted (Fig. 1). Firm

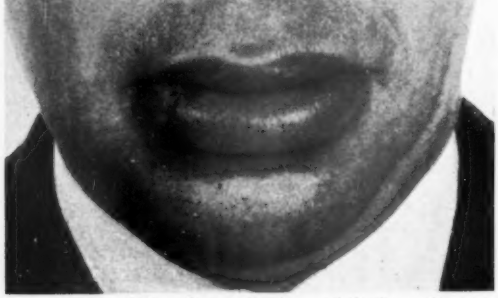

FIG. 1.—Induration and œdema of the lower lip.

induration of elastic consistency extended down to the level of the mucocutaneous junction but did not extend laterally into the cheeks. It has since remained unchanged. The tongue is normal.

General physical examination revealed nothing abnormal in any system. No enlargement of the cervical glands was detected. There was no clinical or radiological evidence of infection of the teeth or upper respiratory tract. X-ray of the chest was normal.

Investigations.—White blood count within normal limits. Mantoux 1 : 1,000 negative.

Biopsy (17.5.55): "A section through the lip shows granulomatous inflammation and œdema in the corium, with dilatation of lymphatics, the cellular infiltration includes lymphocytes, plasma cells, occasional eosinophil leucocytes, occasional foci of giant cells and modified macrophages. On the buccal aspect where the infiltration is greatest it is continuous, but in the rest of the specimen it is focal. The muscle and connective tissue in the deepest part of the specimen is little affected, the epidermis shows acanthosis and hyperkeratosis, especially on the buccal aspect.

"The histological picture is that of a granulomatous lesion of the lip with œdema and dilatation of lymphatics."

Treatment.—Isoniazid was given for several weeks without response and radiotherapy (900 r in 5 divided doses) was also ineffective.

Comment.—We have been able to examine this patient on frequent occasions since shortly after the onset of the swelling. A localized angioneurotic œdema was our provisional diagnosis until the induration developed. The clinical and histological findings conform closely to the granulomatous cheilitis described by Miescher (1945) and by Grzybowski and Jablonska (1949). Opinions differ as to the relationship of this condition to the Melkersson-Rosenthal syndrome in which recurrent facial palsy precedes the swelling of the lip and in which lingus plicata is often present. Apart from the presence of these other manifestations there appears to be no difference between the syndromes (Hauser, 1953). The cheilitis may be associated with similar infiltration of the cheeks which may also occur alone (Braun-Falco and Rathjens, 1953). Hering and Scheid (1954) believe that the Melkersson-Rosenthal syndrome is yet another component of sarcoidosis. In one of their cases a cervical lymph node showed the inclusion bodies of sarcoidosis. Findlay (1954) obtained satisfactory results by resection of the lip and we propose to have this done.

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Postscript (October 1956).—During the last three months the swelling of the lower lip has gradually subsided. When the patient was examined in September the lip was virtually normal in size.—A. R.

Dr. C. D. Evans: Dr. Warin showed a similar case to this Section in 1953. The histology was of a plasma cell granuloma. Since this time the condition has remained unchanged except for reduction in size of the swollen lips following radiotherapy. Recently she had had ulceration of the lips but it is difficult to decide whether this is due to the natural course of the disease or to the radiotherapy.

REFERENCE.—Warin, R. P. (1953) *Proc. R. Soc. Med.*, **47**, 171.

Amyloidosis Cutis.—Arthur Rook, M.D., and Danilo Stevanovic, M.D.

Mr. A. W., aged 65, studhand.

History.—Wounds of the right shoulder and right hand in the First World War resulted in the loss of the index and middle fingers. His health has always been excellent. In April 1955 he observed a slightly irritable patch on the dorsum of the penis. It enlarged steadily for two months, since when it has remained unchanged. For some time before this he had been aware that the right sole was thickened but this had caused him no discomfort. He had not noticed the lesions on his trunk.

On examination.—On the dorsum of the shaft of the penis there is a slightly elevated soft yellowish brown plaque 5·5 × 3·5 cm. in size. When it is not covered by the superficial scaling which is sometimes present, it has a translucent appearance and feels somewhat gelatinous. On the upper left chest are numerous small lichenoid papules of the same colour and consistency as the plaque. There is some irregular and pitted hyperkeratosis of the right sole and the inner side of the foot. The oral mucous mem-

brane is normal. General physical examination revealed no abnormality. The tip of the spleen was palpable, but the liver was not enlarged.

Investigations.—Blood count (29.6.55) within normal limits. E.S.R. (Westergren) 35 mm./one hour—28 mm. corrected. Urine: Trace of albumin; no Bence-Jones protein. Plasma cholesterol 226 mg./100 ml. Serum proteins: Electrophoretic pattern normal. X-ray chest: Heart and lungs normal. Metallic shot in right shoulder region.

Biopsies (Dr. A. M. Barrett).—(1) Penile lesion (20.6.55): "A small piece of skin in which the superficial half of the corium is abnormal. The abnormality is manifested by (*a*) interstitial infiltration by homogeneous weakly eosinophilic substance which stains feebly with mucicarmine and by the methyl violet method for amyloid; (*b*) absence of elastic fibres in the infiltrated area; (*c*) inflammatory cellular infiltration (polymorphonuclear leucocytes and plasma cells) around the capillaries in the affected part of the corium.

"The staining reactions suggest that the abnormal substance is amyloid, which normally stains with mucicarmine, whereas mucin usually fails to give a positive methyl violet test for amyloid. The histological picture is therefore in agreement with the diagnosis of lichen amyloidosis. I think that the inflammatory reaction is greater than usual."

(2) Lesions of shoulder (15.8.55): "A piece of skin in which the epidermis appears somewhat atrophic, and immediately beneath it there is a conspicuous zone of inflammatory cellular infiltration (plasma cells and lymphocytes). This sub-epidermal zone of cellular infiltration has an abrupt, clearly defined lower border; elastic fibres are absent and periodic acid-Schiff staining suggests that there is some abnormality of the connective tissue matrix; but staining with methyl violet and mucicarmine does not provide convincing evidence of the presence of amyloid.

"I think that this lesion may be essentially the same as that in the previous biopsy, although the cellular infiltration is greater and the interstitial deposit much less. The abundance of plasma cells is noteworthy."

Dr. Rook: We thought of the possibility of myelomatosis but of this there is no evidence at present. I do not know whether the lesions on the foot are part of the amyloidosis. We will carry out a further biopsy to establish their nature.

POSTSCRIPT.—Lesion of foot (April, 1956): "Irregular hyperkeratosis. No amyloid deposits" (Dr. A. M. Barrett).

The serum proteins showed a normal electrophoretic pattern and this, in conjunction with other findings, would appear to exclude multiple myelomatosis.—A. R.

The following cases were also shown:,

(1) **Psoriasis with Unilateral Facial Involvement.** (2) **Milker's Nodes.**—Dr. MARK HEWITT (for Dr. ROBERT WARIN).

Poikilodermia Atrophicans Vasculare.—Dr. C. H. WHITTLE and Dr. J. L. MOFFATT.

Linear Lichen Planus.—Dr. R. H. MARTEN (for Dr. SYDNEY THOMSON).

Alopecia Areata Treated with Hydrocortisone.—Dr. W. FRAIN-BELL and Dr. OLIVER SCOTT.

Sarcoidosis with Dermatomyositis.—Dr. R. G. HOWELL and Dr. G. B. MITCHELL-HEGGS.

Mercury Sensitivity Reaction in a Tattoo.—Dr. R. H. MEARA.

[*March* 15, 1956]

Juvenile Dermatomyositis.—C. M. RIDLEY, M.R.C.P. (for BRIAN RUSSELL, M.D., F.R.C.P.).

R. P., aged 2 years 11 months.

History.—Born after a normal pregnancy and delivery, he was well until four months ago. Following a cold he was then found to have periorbital œdema and mottled erythema on the face, neck, buttocks and legs. Shortly afterwards general weakness was noticed and he became very irritable. The muscles appeared to be tender. He has had a temperature of 99–100° F. and a pulse rate of 120 per minute or more since the onset of symptoms. There has been no apparent difficulty in breathing or swallowing.

Treatment.—He has had ACTH and cortisone for three months; the highest dose was ACTH 25 units and cortisone 50 mg. daily. With this dosage he showed improvement in the œdema but in no other respect. Since its withdrawal, the skin lesions have become more marked. We consider he is a suitable patient for treatment with prednisone (*v. infra*).

Past history.—Chickenpox at the age of 16 months.

Investigations.—Chest X-ray normal. Muscle X-ray: no evidence of trichinosis. Blood count normal. E.S.R.: 8 mm. in one hour. Plasma proteins normal. Twenty-four hour urine: No mercury detected; creatine excretion 53·5 mg. (specimen incomplete); no protein, no casts. ECG normal. Biopsies: Muscle (right thigh): Slight perivascular and interstitial lymphocytic infiltration. Skin (right elbow): Superficial scaling and œdema

over fibrotic lesion of skin and subcutis. Purulent crust over area of parakeratosis, acanthosis, and marked œdema in upper dermis. Fibrosis in lower dermis and subcutaneous fat, and moderate perivascular lymphocytic infiltration. No atrophy of dermal appendages.

Present state.—A well-developed, fretful child who seems to dislike the light. He is unable to sit up unassisted or to stand. There is slight puffiness round the eyes. The back shows an increased amount of lanugo hair. On the backs of the knuckles and interphalangeal joints, on the posterior aspects of both axillæ, on the left elbow, over the backs of the metatarsals, on the right foot and over both external malleoli the skin shows a marbled appearance with atrophy, mottled erythema and telangiectasia. There is some diffuse faint erythema elsewhere. There are small red, punctate blanching areas round the root of some finger nails.

Addendum.—When last seen on May 22, 1956, the child was walking unaided and seemed less irritable. The changes over the knuckles persisted. At that date he was on a maintenance dose of 10 mg. of prednisone daily.

Comment.—Several series of cases of dermatomyositis in children have been reported. Wedgwood *et al.* (1953), for instance, report 26 cases and Roberts and Brunsting (1954) 40 cases. Wedgwood *et al.* (1953) say that of their 26 cases (1916–1952) there have been 10 deaths, 8 of them occurring from four to twenty-six months after the onset, 4 still have active disease, 4 have contractures and 8 are normal. No one appears to have described malignancy in association with dermatomyositis of childhood, in contrast to the frequent association of the disease with malignancy in adult patients.

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Skin Reactions at Site of Green and Red Tattoo Marks.—J. A. BONNELL, M.B., B.S. (for BRIAN RUSSELL, M.D., F.R.C.P.).

A. R., aged 41. January 1956: He noticed irritation and pimples on the left leg, left arm and chest at the site of tattoo marks. He was tattooed in Bombay in 1936.

Occupation.—Since 1946 he had been an interior painter and decorator and for two months he had been "dry rubbing down" old lead-painted walls and woodwork. For one month he had also used a chemical paint remover.

On examination.—Widespread tattoos in green, red and black on the chest, arms and legs. There was an obtuse-domed semitranslucent nodulation affecting a part or the whole of a number of the green and a lesser number of the red markings in the tattooed areas (Fig. 1). There was a reaction in 24 green areas, in 3 red areas and by April 9, 1956, there were 2 lesions in areas of untattooed skin enclosed by black tattoo lines.

Investigations.—Radiographs of the chest and hands normal. Plasma proteins and blood count normal. Blood Wassermann and P.P.R. negative. Patch tests to nickel, chrome, cobalt, copper and mercury negative. Mantoux reaction: Negative at 1/1,000, positive at 1/100.

Histological examination (29.2.56): *Biopsy of skin with green tattoo:* Foreign-body granulomatous reaction, resembling sarcoid, to green bi-refringent particles in the dermis. Slight epidermal atrophy (Fig. 2). *Biopsy of skin with red tattoo :* Foreign-body granulomatous inflammation in dermis. Scanty carbon and also scanty brown refractile but not doubly refractile particles. Iron stain negative (Fig. 3). (18.4.56): *Biopsy of skin with no tattoo:* Granulomatous infiltration resembing sarcoid in dermis. One crystal of green pigment similar to that in the area of the green tattoo, a few scattered particles of brown non-refractile pigment giving a negative Perle stain, and some carbon pigment in the granulomas.

Analysis of biopsy for metals (14.3.56): Half the biopsy material taken on 29.2.56 was kept and wet ashed in chrome-free concentrated sulphuric and nitric acids and the resultant solution analysed chemically and by polarography. *Biopsy of green tattoo:* Chemical analysis—800 p.p.m. chromium. Polarography—Large quantities of chromium. *Biopsy of red tattoo:* Chemical analysis—Trace of chromium detected. Polarography—Trace of chromium present.

Treatment.—2.5.56: Hydrocortisone was injected into two of the lesions at green tattoo sites on the chest. Two weeks later there was a definite reduction of the œdema with flattening of the skin at the injected sites. These injections are being repeated.

The pigments commonly used to produce blue-black, red and green colours in tattooing are as follows—Black: carbon, usually in the form of Indian ink, is the most commonly used.

Black iron oxide is also used. Red: cinnabar (mercuric sulphide) is the most popular and widely used red pigment. Sienna, a form of "ochre" which is a natural ferric hydrate and basic ferric sulphate containing alumina, silica and lime, is also a popular red pigment. Green: usually chrome salts, either chromic oxide or chromium sesquioxide. Copper salts, mixed with coal tar dyes such as Hansa yellow, are also used.

Skin reactions at tattoo sites are not uncommon. Usually the reaction occurs immediately after the operation and gradually settles down during the following 2 to 3 days. Tattooing may predispose locally to psoriasis, lichen planus or lupus erythematosus; syphilis and tuberculosis have been acquired by tattooing. Sometimes the skin remains inflamed for several weeks and occasionally the reaction is so severe and persistent that the whole area of tattooed skin may have to be excised. An allergic sensitization to one of the pigments may develop years later. It is not uncommon for reactions to occur in red tattoo marks. The red pigment is usually mercuric sulphide and sensitivity may develop as the result of absorption of small amounts of mercury from amalgam fillings in the teeth, or as the result of therapeutic injections of mercurial diuretics.

Comment.—Our patient was tattooed in 1936 in Bombay. He had no reactions in the tattooed site until one month before attending hospital when he noticed severe itching and œdema confined to the green, and to a lesser extent the red areas of the tattoos.

Rostenburg, Brown and Caro (1950) describe a similar case where after an interval of eight years a reaction occurred at the site of green tattoo marks in the skin. The histological reaction in this case was almost identical with that of our patient.

FIG. 1.—Area of chest showing skin reactions at tattooed sites

The green areas contained large amounts of chromium, confirming that the green pigment was a chrome salt. Surprisingly, no mercury was found in the red area of skin but traces of chromium were present. The inference is that the red pigment used was Sienna. Presumably during the tattooing there was some contamination of the red dye with chromium.

It is interesting to consider why a skin reaction should occur at the tattooed sites in this patient almost twenty years after he had been tattooed. It could be because during the past few months he had been "dry rubbing down" old lead-painted walls and woodwork. All lead pigments in the range pale yellow to deep orange are lead chromates and it seems probably that during the course of his work he may have inhaled sufficient lead chromate dust to cause a sensitivity reaction in the chromates embedded in his skin, both in the green and the red areas of the tattoo marks. The reason why only a small number

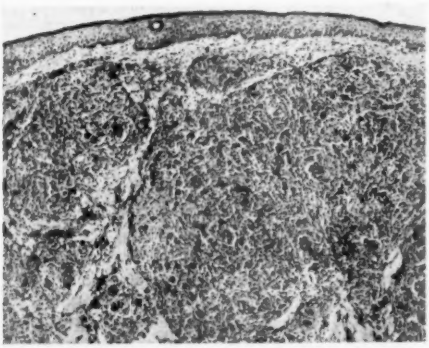

FIG. 2.—Photomicrograph from skin with green tattoo × 36. (*Hæmatoxylin and eosin.*) Showing subepidermal rounded granulomatous foci containing green refractile granules

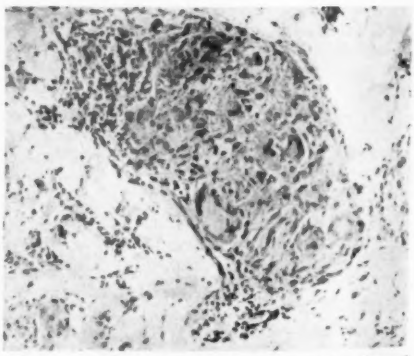

FIG. 3.—Photomicrograph from skin with red tattoo × 111. (*Hæmatoxylin and eosin.*) Showing non-refractile pigment granules and details of a sarcoid-like granuloma.

of red areas had reacted, and even then to a lesser degree than the green, was due to the fact that the chrome was only present in the red areas as a contaminant. On the other hand not all the green areas have reacted.

Finally sarcoid-like lesions have been reported as occurring at the site of the implantation of silica and certain other inorganic elements particularly beryllium in the skin. The histological picture in this patient was sarcoid-like but the intracellular refractile granules characteristic of sarcoidosis were not present and the lymphocytes and giant cell proliferation surrounded the implanted tattooing material. There was no evidence of lesions of sarcoidosis elsewhere in the body, chest and hand X-rays were normal, the plasma proteins and blood counts were normal and the Mantoux reaction was positive at 1/100. There are many points against a diagnosis of leprosy.

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POSTSCRIPT (20.6.56).—Two green areas on the side of the chest have resolved following the injection of hydrocortisone. There is atrophy of skin at these sites. In addition the majority of the affected areas are resolving spontaneously which is against the diagnosis of sarcoidosis.—J. A. B.

Hydroa Gravidarum.—HAROLD WILSON, M.R.C.P.

History.—Mrs. S. B., aged 25, first noticed a rash in May 1955, being at the time three months pregnant. The rash began as a few red macular areas on the inner sides of both wrists. A few days later a few small raised itching urticarial wheals appeared on the thighs, forearms and subsequently on the neck and trunk. A week after the onset of the rash large numbers of blisters varying from ¼ in.–1 in. in diameter appeared all over the body surface. In spite of this the general health remained good. Except when controlled by cortisone blisters have continued to appear regularly. A female child weighing 9 lb. was born on November 11, 1955.

Past history.—Measles, mumps and ? rickets in infancy. Vincent's angina when aged 20.

Family history.—Mother and father alive and well. Only child.

Married.—1 daughter aged 2 born after normal pregnancy.

On examination.—The rash consists of erythematous patches, wheals and blisters. Chest and heart: N.A.D. B.P. 130/70. Abdomen: N.A.D. C.N.S.—N.A.D. Urine: Albumin negative. Sugar negative.

Investigations.—Biopsy: The epidermis shows hyperkeratosis and thickening. There are a number of bullæ, mostly intra-epidermal, but some sub-epidermal; cleavage does not occur at the basal layer. The exudate in the bullæ contains neutrophils and a conspicuous number of eosinophils. The dermal papillae are œdematous and contain many eosinophils. More deeply, there are perivascular collections of inflammatory cells, mostly lymphocytes and plasma cells, with some eosinophils. The picture suggests dermatitis herpetiformis, or a rather atypical bullous form of erythema multiforme.

Treatment.—The patient was admitted to hospital on May 15, 1955. After five days' rest in bed there had been no improvement in the eruption; so cortisone 25 mg. four times daily was started on May 20. Three days later no fresh blisters had appeared. There was a minor exacerbation on June 3, 1955, after reduction of cortisone to 25 mg. b.d. with clearance of the rash when the dose was raised to 25 mg. t.d.s.

In June and July diaminodiphenylsulphone 50–100 mg. daily was given but discontinued when blisters reappeared. In the subsequent six months blisters continued to appear but were usually controlled by cortisone 25 mg. or prednisolone 5 mg. t.d.s. Diaminodiphenylsulphone 100 mg. daily and subsequently sulphapyridine 0·5 gram t.d.s. had no effect on blister formation.

Comment.—This patient has had two female children. She developed the disease in the second pregnancy but not in the first. This condition is frequently called dermatitis herpetiformis but is not entirely typical of it. The flexures of the arms have been consistently affected while the buttocks and shoulders have usually remained relatively free of lesions. Large bullæ have been common and the erythematous patch studded with vesicles which one sees frequently in dermatitis herpetiformis has not been a common feature of this case.

Attempts to control the condition with sulphones and sulphapyridine have been consistently ineffective. In view of her pregnancy I was hesitant about treating her with cortisone or prednisolone but although she was on these drugs for a period of six months, she delivered a normal healthy female child at term. The rash has persisted for four months since then, but is now beginning to fade.

Dr. Brian Russell: Herpes gestationis is a rarity but at present we have three cases under observation at the London Hospital. One patient is pregnant, the other 2 have recently been delivered but the disease remains active. There have been 11 cases at the London Hospital since 1921, an incidence of one for every 3,000 to 3,500 deliveries. The histology of herpes gestationis is the same as that of dermatitis herpetiformis. This does not prove that herpes gestationis is a variant of dermatitis herpetiformis. It is more nearly akin to erythema multiforme bullosum. In distribution, herpes gestationis tends mostly to affect the limbs, particularly the distal parts, but it may also appear widely on the trunk. The face is usually spared but two of our patients had mucosal lesions. The lesions of herpes gestationis are characteristically polymorphic: they are papulovesicular, later becoming erythematous and polycyclic with bullæ only involving some parts of the erythematous patches. The bullæ of dermatitis herpetiformis are often accompanied by little or no erythema.

None of the 11 patients had ever suffered from a bullous eruption between pregnancies, except for the highly characteristic exacerbations within forty-eight hours of delivery and just before a few of the following menstrual periods.

Dermatitis herpetiformis may affect children, men, or women of child-bearing age. In older men and women, if it occurs at all it takes on the different clinical features and altered therapeutic responses of senile dermatitis herpetiformis or pemphigoid, a disease which also seems more akin to erythema multiforme bullosum.

I have examined the case notes of 8 women of child-bearing age who have suffered from dermatitis herpetiformis. In no case was there a record of exacerbation during pregnancy. One woman, aged 40, who had had dermatitis herpetiformis for ten years was observed throughout a pregnancy as well as for several years before and after. Throughout the pregnancy the dermatitis herpetiformis continued, sometimes a little better, sometimes a little worse, just as it had before she was pregnant. Three months after delivery it was continuing as before and two years later it was reported to be in a more severe phase, though responsive to sulphapyridine. Dermatitis herpetiformis usually responds briskly to dapsone or sulphapyridine. Our 3 patients with herpes gestationis have not responded to these drugs. On the contrary, 2 patients worsened while taking dapsone. Exacerbations also occurred when œstrogens were given to suppress lactation in 2 of 3 patients. Progesterone injections helped one patient, had no effect on a second and seemed to aggravate a third. All 3 patients have benefited from ACTH and cortisone.

The disease usually starts in the second trimester, sometimes in the third or even in the puerperium. Steroids can be given after three months of pregnancy without any fear of causing any developmental abnormality in the fœtus. It is advisable to tail off the dosage well before delivery, lest the infant should need supportive therapy. Fortunately the disease tends to abate spontaneously towards the end of pregnancy, only to flare up again soon after delivery.

The 11 patients had produced 22 live children after pregnancies complicated by herpes gestationis and there had been 6 miscarriages or stillbirths, between 17 weeks and 33 weeks of pregnancy. One woman had had four of these stillbirths.

The concept that herpes gestationis is related to some abnormality of chorionic activity is not supported by the finding of negative rat tests in 6 patients in the puerperium at times when the disease was still active.

The President: Hydroa gravidarum may relapse earlier with each subsequent pregnancy. The subsequent attacks tend to be progressively more severe and the duration after parturition more prolonged. The causal factor probably resides in the fœtus or placenta which could easily supply sensitizing substances to which the mother forms antibodies. The antibody response might be expected to occur earlier and to a greater level, with each pregnancy.

The placenta may furnish these sensitizing or toxic factors. This was suggested by Elliott (1938) when recording a case of a bullous eruption occurring with chorion epithelioma. The persistence of placental villous elements in the uterine wall could be assumed if gonadotrophic hormone was found in the urine in those cases where the blisters appeared for several weeks or months after parturition. I have seen the blisters persist for a year after parturition.

REFERENCE.—ELLIOTT, J. A. (1938) *Arch. Derm. Syph., Chicago*, **37**, 219.

A short paper on **Rhinoplasty and Diseases of the Skin** was read by Mr. CHARLES HEANLEY. The following cases were shown to illustrate Mr. Heanley's paper:

(1) **Rhinoplasty for Carcinoma on Lupus Vulgaris.** (2) **Rhinoplasty for Sarcoma on Lupus Vulgaris.**—Mr. CHARLES HEANLEY and Dr. BRIAN RUSSELL.

Rhinoplasty for Old Gumma of Nose and Palate.—Mr. CHARLES HEANLEY and Dr. AMBROSE KING.

The following cases were also shown:

Purpuric Lichenoid Dermatitis.—Dr. J. S. PEGUM.

Lupus Erythematosus Arising on the Site of Previously Treated Lupus Vulgaris.—Dr. N. A. THORNE.

Nodular Panniculitis with Atrophy.—Dr. PETER SMITH (for Dr. BRIAN RUSSELL).

Connective Tissue Nævus.—Dr. C. M. RIDLEY (for Dr. BRIAN RUSSELL).

Hypertrichosis Lanuginosa (Two Cases).—Dr. J. E. M. WIGLEY.

Carotinæmia.—Dr. E. LIPMAN COHEN.

Necrobiosis Lipoidica Diabeticorum improving under Treatment with Local Hydrocortisone Injections.—Dr. P. J. HARE.

Acanthosis Nigricans Juvenilis.—Dr. C. D. CALNAN.

Polycythæmia with Gangrene of Fingers.—Dr. CLARA M. WARREN.

Section of Endocrinology

President—A. C. CROOKE, M.A., M.D.

[*October* 26, 1955]

THE Presidential Address read at this Meeting by A. C. Crooke, M.A., M.D., on "The Measurement of Pituitary Function" was published in the *Lancet*, (1955) ii, 1045.

[*February* 22, 1956]

A JOINT MEETING was held between the Section of Endocrinology and the Society for Endocrinology. The meeting took the form of a Symposium on "Selected Aspects of Hormone Administration in Animals and Man". The titles of the papers presented were as follows:

Treatment of Adrenocortical Insufficiency.—Dr. J. D. NABARRO.
Treatment of Hypothyroidism.—Dr. T. RUSSELL FRASER.
Role of Hormone Administration in the Control of Lactational Performance.—Dr. B. A. CROSS.
Abnormalities of the Human Breast.—Dr. G. L. FOSS.
Diagnosis and Therapy of Endocrine Disorders in Farm Animals.—Dr. L. E. A. ROWSON.
The Use of Androgens in Women.—Dr. G. I. M. SWYER.
The Administration of Œstrogens and Progesterone to Monkeys.—Dr. P. L. KROHN.
The Use of Œstrogens in Chickens and Turkeys.—Dr. W. P. BLOUNT.

Abstracts of these papers appear in the *Journal of Endocrinology*, **14**, i, August, 1956.

[*March* 28, 1956]

Hypopituitarism Following Sinusitis and Cavernous Sinus Thrombosis.—EIRIAN WILLIAMS, M.D., M.R.C.P. (for DONALD HUNTER, M.D., F.R.C.P.).

J. A., male aged 56. Admitted August 2, 1951.

History: Eight days: pain above and behind left eye following a cold. Four days: severe left frontal headache with vomiting. One day: left eyelids swollen.

On examination.—No pallor. T. 99·5° F. Tongue coated; long filiform papillæ. B.P. 130/80. Left eye: Œdema of lids and of soft tissues of cheek. Conjunctival injection. No proptosis. Tenderness on pressure above and below the orbit. Ocular movements—weakness of elevation and abduction.

Skull X-ray: Enlargement of sella turcica with erosion of floor and dorsum sellæ.

C.S.F. Protein 60 mg.%, otherwise normal.

Carotid angiograms normal.

Progress.—Total left ophthalmoplegia developed within forty-eight hours and three days later movements of the right eye became impaired. He was treated with antibiotics and anticoagulants, the right eye returned to normal within four weeks and the left, apart from slight limitation of abduction, within three months.

March 1952: Easily tires with pains in the shoulders and arms. Observed to be pale, but Hb normal. He became impotent, with loss of body hair, and although he shaved daily his beard was soft.

October 1955: Three recent near-fainting attacks. Soreness of tongue and mouth.

On examination.—Marked pallor. Myxœdematous facies. Skin dry, smooth and soft. No body or axillary hair, scanty pubic hair. Tongue red with atrophic mucosa. Angular stomatitis. B.P. 120/70. 17-ketosteroid excretion 4·8 mg., 5·7 mg. Radio-iodine uptake by thyroid low; increased following administration of thyroid stimulating hormone. Skull X-ray: Partial recalcification of sella which is now normal in size. Visual fields normal. Hb 77%. M.C.V. 86 cu.μ. Fractional test meal: free acid present.

Treated with testosterone and thyroid. Tongue improved rapidly when cortisone added.

Comment.—The onset of this patient's hypopituitarism was clearly related to his acute infection, and the subsequent recalcification of his sella turcica makes an alternative diagnosis of pituitary tumour unlikely. Dimsdale and Phillips (1950), describing four patients with ocular palsies due to nasal sinusitis, showed that in each there was erosion or destruction of the floor and dorsum of the sella turcica. Recovery of visual symptoms followed drainage of the infected sinus and the radiological appearances of the sella also improved. Hypopituitarism was not observed on follow-up six months to five years later.

The anæmia of hypopituitarism was reviewed by Summers (1952). He found few recorded instances of an associated glossitis and none of angular stomatitis, both features being present in one of his own cases. The anæmia is usually refractory although Sheehan and Summers (1954) commented favourably on the value of cortisone. In our patient it produced rapid healing of his glossitis and stomatitis, but it is early to assess its hæmatinic effect.

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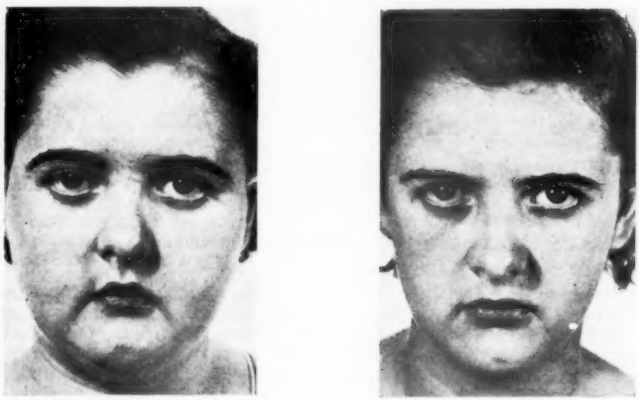
SHEEHAN, H. L., and SUMMERS, V. K. (1954) *Brit. med. J.*, i, 723.
SUMMERS, V. K. (1952) *Brit. med. J.*, i, 787.

Cushing's Syndrome, Relapsing Twice after Surgery.—M. H. LESSOF, M.R.C.P., and P. M. F. BISHOP, D.M.

Miss P. W., aged 24.

History.—At the age of 16, noticed striæ of the abdomen and thighs, obesity, frontal headaches and amenorrhœa. Three years later she was referred for examination because of a sharp pain in the left thigh.

On examination.—Obesity of the trunk and face (Fig. 1A); purple striæ; several bruises and patches of purpura; a growth of hair on the face; and blood pressure of 160/120.

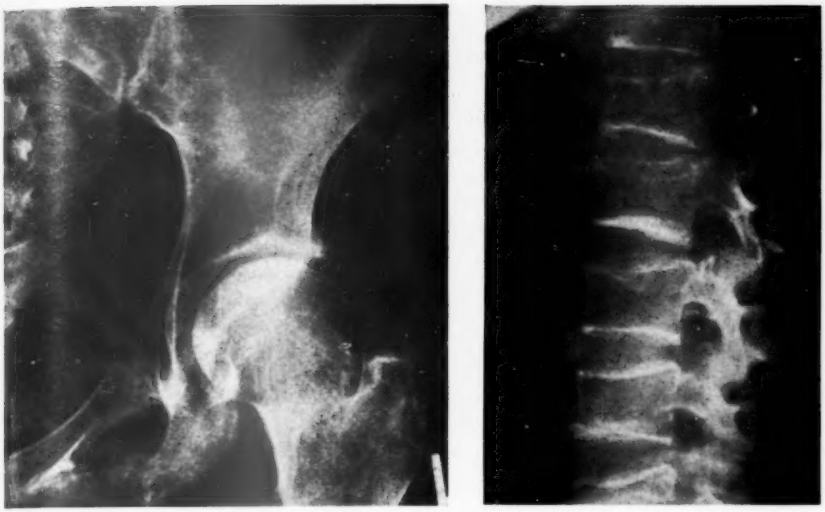


A B

FIG. 1.—Appearance of the patient before operation and six months after the second stage of a subtotal adrenalectomy.

Investigations.—The pain in the thigh was attributed after investigation to osteoporosis and fractures of the pelvis (Fig. 2A, B). She also had glycosuria and a lag type of glucose tolerance curve. Tomograms taken after a perirenal insufflation of air showed no tumour on either side.

Treatment and progress.—Mr. F. N. Glover subsequently removed two-thirds of the right adrenal and the whole of the left adrenal, and the patient had a remission of symptoms lasting two years. She has since relapsed on two occasions. On the first, 3·8 grams of a regenerated hyperplastic right adrenal were removed and deep X-rays were given to the pituitary in doses totalling 3,500 r. On the second, the remainder of the gland was removed, because of a recurrence of hypertension, headaches, obesity and amenorrhœa. She was maintained on 25 mg. of cortisone daily between operations and is now taking 37·5 mg. of cortisone a day.



A B

FIG. 2.—X-rays showing A fractures of the ischium and pubis, B osteoporosis of the lumbar vertebræ, with wedging and Schmorl's nodes.

Comment.—The amount of adrenal tissue which must be removed to effect a cure of Cushing's syndrome varies from patient to patient. In mild cases with bilateral adrenal hyperplasia, removal of a part or the whole of one gland may be sufficient (Bishop *et al.*, 1954). More often a bilateral operation is necessary with the removal of between five-sixths and nine-tenths of all adrenal tissue. A high proportion of these cases subsequently require maintenance therapy with cortisone, as reported by Sprague (1953). It is thus an accepted disadvantage of the method that atrophy of the residual gland tissue may occur.

In the present case there was a recurrence of adrenal hypertrophy on two occasions despite surgery, radiotherapy to the pituitary, and post-operative maintenance therapy with cortisone. This emphasizes a second disadvantage of subtotal adrenalectomy, which is the risk of recurrence.

The experience of this case and one other post-operative recurrence leads us to suggest that total bilateral adrenalectomy should be performed for selected severe cases of Cushing's syndrome and for all recurrences after treatment. Excluding the present case, 3 out of the last 9 patients operated on by Mr. F. N. Glover have been so treated.

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Pretibial Myxœdema with Severe Exophthalmos.—GERALD BLANSHARD, M.D., M.R.C.P. (for DAVID FERRIMAN, D.M., M.R.C.P.)

Miss E. N., aged 20.

History.—She grew nervous and her eyes became prominent following an appendicectomy in June 1952. Goitre appeared following tonsillectomy in March 1953. No family history of thyroid disorder. She was seen in February 1954 and found to be nervous with a considerable goitre, a pulse-rate of 132/minute and exophthalmos. After preparation with propyl thiouracil followed by iodine she had a partial thyroidectomy performed on 22.6.54 (Mr. T. H. Hennebry). Sections of the thyroid showed a little lymphadenoid infiltration.

In March 1955 her exophthalmos became more severe, and pretibial myxœdema appeared, mainly affecting the anterolateral aspect of the left shin. She appeared euthyroid. She has been treated with thyroid 1 grain daily, raised later to 2 grains daily, and with deep X-ray to the orbits (Dr. E. W. Emery). A little recession of the left eye has occurred. She has a little conjunctival irritation but there is no ophthalmoplegia (Fig. 1).

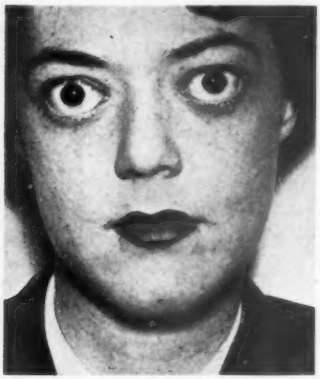

FIG. 1

The association of severe exophthalmos with pretibial myxœdema seems common, and these may both be dependent on the same mechanism. Severe exophthalmos appears unrelated either to the functional state of the thyroid, or to the level of circulating thyrotrophic hormone (Gilliland and Strudwick, 1956). It may depend upon the production of "exophthalmos producing substance" by the pituitary (Dobyns and Steelman, 1953). Various forms of treatment have been suggested, including local injection of hyaluronidase, oral thyroid (to depress pituitary function), cortisone (for local or central action), deep X-ray to the skin, orbits or the pituitary, and certain surgical procedures. None of these has proved entirely satisfactory.

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Xanthoma Diabeticorum and Lipæmia Retinalis.—ARNOLD BLOOM, M.D., and M. F. CROWLEY, B.Sc.

A. M. H., bus conductress, aged 29, presented with one year's history of gradually increasing polyuria, polydipsia, polyphagia, lassitude and loss of weight; more recently, amenorrhœa, paræsthesia, pain and weakness in legs. Diet high in fat, ½ lb. butter consumed every two days, almost all food fried. No diabetes in family.

On examination.—Height 64 in., weight 89 lb., wasted appearance, body fat depleted. Reduced reflexes and vibration sense in legs. Crops of small papules, red in colour with yellow centre, on shoulders, elbows, knees and calves (Fig. 1).

Fundi: Retinal vessels pure white (Fig. 2).

Urine: Sugar and acetone present.

Blood: Chocolate colour, serum milk-white on standing.

Investigations.—Glucose tolerance curve: blood sugars fasting 205; then 326, 385, 368 mg./100 ml., 30, 60 and 150 minutes after ingestion of 100 grams glucose.

Total plasma protein 4·7%, A/G ratio 2 : 1. Serum cholesterol 1,458 mg.%. Serum lipids 15,100 mg.% (normal about 500 mg.%).

Paper electrophoresis: (*a*) proteins: normal pattern; (*b*) lipids and lipoproteins: very dense deposit extending from origin to α_2-globulin front: β-lipoprotein not seen as separate band. Cholesterol was found to be distributed throughout the lipid-staining zone.

Section of nodule in skin of elbow (scharlach R stain): lipoid-laden histiocytes and some extracellular lipoid in dermis, consistent with resolving xanthoma.

Treatment.—Soluble insulin four-hourly for two days, then a mixture of soluble and protamine zinc insulin each morning.

Progress.—Fundal vessels became normal in colour and urine became acetone free within forty-eight hours. The serum was only slightly opalescent after this time and was clear two days later. The xanthoma gradually faded but was visible until three weeks after admission. The blood cholesterol fell to 568 mg./ml. after one week, to 262 after two weeks and later to 166. Total plasma proteins rose to 6·1% three weeks after admission. Paper electrophoresis showed a normal pattern two months later.

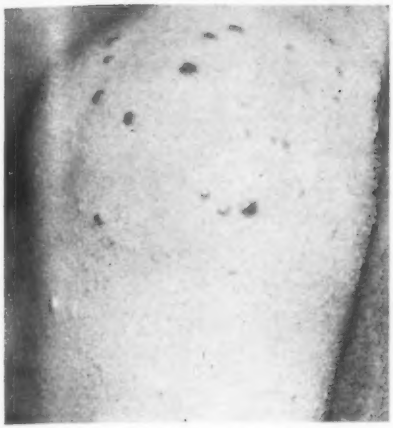

FIG. 1.—Xanthoma of shoulder.

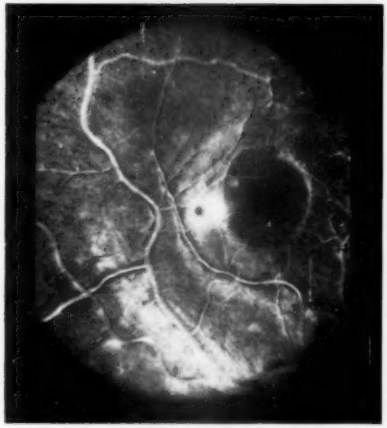

FIG. 2.—White retinal vessels.

Comment.—This diabetic hyperlipæmia is due to a rise in neutral fats and probably represents an increased mobilization of fats from the tissue depots in an attempt to supply the energy needs of the body from fatty acid and ketone body oxidation. A deficient β-lipoprotein formation may also be a factor. Presumably this degree of hyperlipæmia is seldom seen because acidotic coma usually supervenes first; in this case the patient's diet was high in fat. Both the xanthoma and the lipæmia retinalis are expressions of hyperlipæmia and may occur in conditions other than diabetes. Probably the ophthalmoscopic appearance is due to droplets of fat accumulating close to the walls of the arteries and veins, leaving the erythrocytes in the axial stream.

Thyroid Carcinoma in Hypopituitarism with Complete Thyroid Failure.—H. K. IBBERTSON, M.B., M.R.C.P., M.R.A.C.P., and RUSSELL FRASER, M.D., F.R.C.P.

N. C., female, aged 43 years.

Normal health and previous pregnancies until 1938 when sixth pregnancy was complicated by placenta prævia and severe postpartum hæmorrhage. Lactation failed to develop. Periods scanty but regular for one year. Amenorrhœa since then with lassitude, depression, memory impairment and weight gain. Examination in 1950 revealed pallor, scanty pubic and absent axillary hair. B.P. 110/80. Investigations confirmed hypopituitarism with complete thyroid failure:

Serum cholesterol 390 mg./100 ml. B.M.R. −24%. ECG low voltage. Flat T waves. ^{131}I test: Forty-eight-hour neck uptake 10%. Forty-eight-hour urine output 84%. "T" factor 0·8. After five days' thyrotrophic hormone injections (Thyrotropar Armour 10 units daily): Forty-eight-hour neck uptake 25%. Forty-eight-hour urine output 50%. "T" factor 2·6.

Water diuresis. Four-hour excretion 10% dose (max. hourly vol. = 44 ml.). Four-hour excretion (three hours after 50 mg. oral cortisone) 70% dose (max. hourly vol. = 175 ml.).

Insulin tolerance: Hypoglycæmia unresponsiveness.

Urine 17-k. 1 mg./twenty-four hours.

At this time also, there was evidence of a hæmolytic anæmia (spleen palpable) with Hb 10 grams%, and reticulocytes 16%, serum bilirubin 1·2 mg.% and direct Coombs test negative. The ætiology of the anæmia was obscure but because of its progression the spleen was removed in March 1950 with return of the blood picture to normal. Since then, maintained on cortisone 25 mg. and l-thyroxine sodium 0·2 mg. daily.

December 1955 a lump appeared on the left side of the neck and grew steadily in size. Examination revealed a fixed hard mass extending across the mid-line in the region of the thyroid isthmus. A left Horner's syndrome was also present (Fig. 1).

A drill biopsy of the mass revealed an undifferentiated thyroid carcinoma (Fig. 2).

Treatment.—Deep X-ray therapy (3,700 r 23.12.56–26.1.56) caused rapid reduction in size of the mass but within four weeks there was clinical recurrence.

Surgical exploration (26.3.56). Inoperable thyroid carcinoma extending deeply backwards towards the vertebral column.

FIG. 1.—The patient with the approximate extent of the tumour outlined. A slight left ptosis persists.

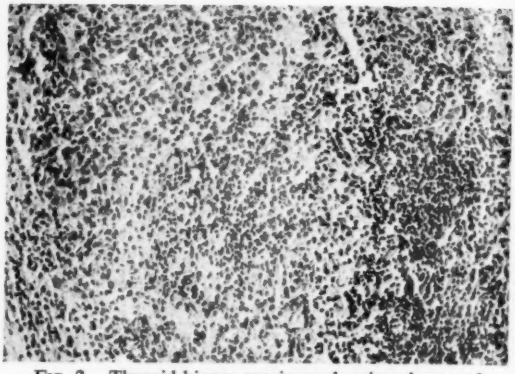

FIG. 2.—Thyroid biopsy specimen showing clumps of anaplastic tumour cells. ×108.

Comment.—The occurrence of thyroid carcinoma in the presence of pituitary failure is of considerable interest. The uncontrolled growth of a neoplasm might be expected to occur in tissues exposed to at least normal endocrine influences. Thyrotrophic hormone could not be demonstrated in the serum of this patient by a standard method of assay (Dr. I. C. Gilliland). In addition, injection of thyrotrophic hormone caused only partial thyroid response indicating that actual atrophy had occurred in a gland deprived of its normal pituitary stimulus.

We have been unable to find reports of thyroid carcinoma occurring under these conditions. Neoplasms in sites other than the thyroid certainly occur in hypopituitarism. The second patient described by Simmonds (1914) died of carcinoma of the stomach, and 9 of Sheehan and Summers' (1949) original 95 patients developed carcinomas at various unspecified sites. Hypopituitarism does not therefore appear to confer an immunity in this respect.

The rapid recurrence of the tumour in this patient following X-ray therapy indicates a poor prognosis. There is no evidence to suggest that the hypopituitary state has in any way modified the tumour growth.

The sequence of events here casts doubt on the value of hypophysectomy as an ancillary method of treatment of thyroid carcinoma.

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Dr. A. Stuart Mason stated that he had seen a similar occurrence of a neoplasm of the thyroid —in this particular instance a sarcoma—arising in a patient with severe pan-hypopituitarism of long standing who had been under treatment with cortisone and thyroid for 3 years.

BOOK REVEIWS

Galen on Anatomical Procedures. Translation of the surviving books with introduction and notes. By Charles Singer. (Pp. xxvi + 289; illustrated. 37s. 6d.) Oxford University Press. London: Cumberlege. 1956.

In the introduction to this work the translator writes "I believe that the text was taken down in shorthand and that it repeats substantially the actual words of Galen. There is no comparable work in ancient literature". Professor Singer has done the medical profession a great service in making these lectures available to English-speaking readers. Not only does the book show us the considerable amount of detailed anatomy known before the Renaissance, but incidentally it furnishes us with a lot of interesting information as to how human anatomy was learnt. Though most dissections were performed on monkeys (both live and dead) we learn that opportunities were taken to dissect the bodies of human enemies slain in battle or those of "men condemned to death and thrown to the wild beasts, or brigands lying unburied on a hillside". Sometimes the bodies of exposed infants were dissected.

Galen frequently takes the opportunity to bring in a clinical case bearing on the anatomical part described; thus he relates an interesting case in which a wrestler received a blow on the sternum which was followed by necrosis. Galen removed the dead bone and though the heart was exposed the patient made a good recovery. Physiologists will be interested to read Galen's account of his experiments on the spinal cord and his careful discrimination of the results.

The book contains a series of 26 figures which elucidate the text, and the translator has added fifteen pages of valuable notes. The translation reads well and the modern names of the muscles and viscera are inserted in brackets after their description. In most places the description is clear and easy to follow. This book should be in every medical library.

Textbook of Endocrinology. Edited by Robert H. Williams, M.D. 2nd edition. (Pp. xii + 776; 173 figs. 91s.) Philadelphia and London: W. B. Saunders Company. 1955.

The plethora of articles on endocrinology is paralleled by that of textbooks on the subject and the prospect of reviewing yet another is not inviting. This volume, however, is fascinating from cover to cover. It is written by a group of ten leading American Authorities in various fields of Endocrinology and the different chapters are almost uniformly readable, comprehensive and up to date. Each gland is dealt with in a separate chapter in which is set out its anatomy and physiology at some length. This is particularly valuable to the student and practitioner who cannot hope to digest the enormous amount of literature on these matters which appears each year, yet some knowledge of this fundamental work is essential if he is to be able to appreciate the significance of various symptoms and signs, the value of new tests or the objectives of new forms of treatment.

In a work of this size it is easy to find fault with isolated statements. Thus it is said that the disease that is the most difficult to differentiate from Simmonds's disease is anorexia nervosa. Surely such a statement is archaic? It seems curious to find the term Simmonds's disease used in the broad sense and Sheehan's disease as a sub-heading for patients with post-partum pituitary necrosis since Simmonds's original case should presumably qualify for this title of Sheehan's disease. In another place it is stated that hyalinized forms of basophil cells in the anterior lobe of the pituitary gland are often increased in Addison's disease to a point where they are more common than the normal type—surely another misstatement?

Only one chapter strikes a grating note, the chapter on neuro-endocrinology. It has long been fashionable to blame "the glands" for any condition which has no known cause, and the psychiatrist has made great play with "the glands" in recent years. The section dealing with adiposo-genital dystrophy, in particular, does not conform with the ideas of most endocrinologists in this country and the suggestion that such cases should receive chorionic gonadotrophin is alarming. Fortunately, it is followed by an excellent chapter on obesity which puts the matter in perspective.

The book contains a number of misprints but, altogether, it is an excellent piece of work.

Diseases of the Nose, Throat and Ear. By I. Simson Hall, M.B., Ch.B., F.R.C.P.Ed., F.R.C.S.Ed. 6th edition. (Pp. xii + 464; illustrated. 20s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

This excellent textbook was first published in 1937 and it has now reached its sixth edition. There have also been two reprints during this period. This tells the story of its popularity, which is well deserved.

It is a formidable task to compress a description of diseases of the ear, nose and throat into 450 small pages. Mr. Simson Hall has done this admirably, but inevitably this compression has led to some omissions which the reviewer regrets and some misleading sentences which need a qualifying sentence to make the meaning clear to a student. There are some statements which are wrong. For example, on page 31, a short anæsthetic such as ethyl chloride or sodium pentothal is recommended for reduction of a fractured nose. No mention is made of protection of the airway from the aspiration of blood. This is a serious omission in a textbook for students and dangerous advice for casualty officers.

Other criticisms in detail can be made but these do not detract from the value of the book as an introduction to the subject. Mr. Simson Hall is to be congratulated on maintaining the high standard he set himself in this book and on keeping it up to date with the changes in surgery.

This book can be recommended as an excellent introduction to the subject for students and an easy means of keeping abreast of changes for the general practitioner.

Obstetrics and Gynæcology for Nurses. By G. W. Garland, M.D., M.R.C.O.G., and J. M. E. Quixley, S.R.N. (Pp. xii + 188; 58 figs. 10s. 6d.) London: English Universities Press Ltd. 1956.

This book, written by an obstetrician in collaboration with a sister-tutor, deals with the subject of Obstetric and Gynæcological nursing from a valuable dual standpoint whose importance is noticeable in the text. It is a short book, a fact realized when recent and similar books extend to five times its size. Yet it contains a great deal of sound information, largely adequate for the nurse's equipment in these branches. This success has been achieved by careful selection, concise compilation, and clear language. The ample glossary will prove valuable for quick reference and is to be commended for its comprehensiveness and precision. Clear anatomical details of the female genitalia and a comprehensive physiology of menstruation are followed by a consideration of the signs and symptoms of normal and abnormal pregnancy, labour, and the puerperium. The obstetric section could be improved by a more ample consideration of the phenomenon of infection and by fuller details of the management of labour, together with their rationale. The chapter on abortion and ectopic pregnancy will prove of much practical service.

The gynæcological section deals comprehensively with menstrual disorders, with dyspareunia and with infertility. It is a moot point whether the therapeutic uses of œstrogen should be so often mentioned without an enjoinder that its administration should be under medical supervision alone. Genital infection, its recognition, sequelæ and especially treatment, is well covered and displacements likewise clearly explained. The practical approach to these sections is equally reflected in the chapters dealing with the description and treatment of the various neoplasms of the genital tract.

With regard to post-operative care, some may not agree that douching should be commenced on the fourth day after a Manchester operation, whilst others would interdict the use of an enema if required on the fifth morning, should the patient have been submitted to a complete repair.

The book is excellent value, well produced, sound and though not an extensive treatise of the subject at least a sufficient one for most needs. It is commended to all nurses who may well find it both a help and a stimulus in their career.

Diseases of the Chest. By H. Corwin Hinshaw, M.D., Ph.D., and L. Henry Garland, M.B., B.Ch., (Pp. x + 727. Illus. 105s.) Philadelphia and London: W. B. Saunders Company. 1956.

This comprehensive textbook on diseases of the chest, written jointly by a professor of clinical medicine and a professor of radiology, bears witness to the tremendous importance of chest radiology and its valuable contributions to modern knowledge of intrathoracic disease. The book summarizes current knowledge and the recent advances on this subject, and there are authoritative chapters on all the common diseases of the chest, excluding diseases of the heart.

Although in the preface the importance of history taking, symptoms and physical signs in relation to diagnosis are emphasized, it is questionable whether these aspects receive

quite their due attention in the main text of the book. The chapter on diagnostic radiology is, however, comprehensive and highly instructive. The text is interspersed with X-ray illustrations, all negative prints, on the whole of a high standard.

The importance of segmental anatomy and pulmonary physiology is recognized, and the chapters on these subjects are good. The chapters on asthma, bronchitis, emphysema and the pneumonias are valuable, as are also those on bronchogenic carcinoma and other intrathoracic tumours. Present-day management of pulmonary tuberculosis is evolving so rapidly that the seven chapters devoted to this subject are, on the whole, well balanced and comprehensive. Special attention is given to the questions of home versus hospital treatment, specific drug therapy and its duration, collapse therapy, pulmonary resection, &c. It is interesting, and indeed pleasing, to note the full attention given to all forms of collapse therapy and to the concept of tuberculosis as a generalised disease. In this connexion, one welcomes the recognition of the need for adequate post-operative medical treatment, following excisional surgery.

There are few major omissions in this work, and the chapters on the pneumokonioses, the pneumomycoses and sarcoid are particularly worth while, as is also the one on collagen diseases, a subject which receives its due attention.

On the whole, although the opinions enunciated may differ in some respects from those commonly held by British physicians, they are sound and well balanced, and the book has undeniably kept pace with modern developments. The bibliography contains few references to British literature, and one would like to see a number of printer's errors corrected in a future edition.

Peripheral Vascular Disorders. Edited by Peter Martin, V.R.D., M.Chir., F.R.C.S.Ed., R. Beverly Lynn, M.D., F.R.C.S., J. Henry Dible, M.B., LL.D., F.R.C.P., and Ian Aird, Ch.M., F.R.C.S. (Pp. viii + 847; 568 figs. £5 10s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

The appearance of this excellent textbook will be welcomed by general surgeons who are increasingly called upon to care for peripheral vascular disorders.

The first chapter minutely describes the innervation of the peripheral blood vessels and is in itself a valuable monograph on Professor G. A. G. Mitchell's painstaking researches in this field, a fact which probably justifies its inclusion, although the subject is treated in more detail than the practising surgeon is likely to assimilate.

There does not appear to be the same reason for the second chapter describing the gross anatomy of the peripheral vessels which mainly repeats the information readily obtainable from any anatomical textbook. Space could have been more usefully occupied by a description of the surgical approach to the vessels.

The chapter on the physiology of the blood-flow in the limbs would have been made more readable and no less useful by the omission of much experimental detail, particularly since—as the author himself states—full comprehension often requires reference to the original papers, many of which are, fortunately, in English.

The chapters on the pathology of atherosclerosis and of Buerger's disease bear the stamp of Professor J. H. Dible's original work on the correlation of histological changes with the radiological appearances of amputated limbs after injection of the vessels.

A full description of all the organic and functional disorders of the peripheral vessels, arterial, venous and lymphatic, is given, and illustrated by abundant photographs generally well selected and reproduced. It is doubtful, however, whether so many illustrations of ischæmia in its various phases ranging from colour changes of the skin to massive amputations justify the space they occupy. Had their number been reduced and the introductory chapters pruned this bulky volume would have gained more in manageability and cheapness than it would have lost in completeness.

In the surgical treatment of obliterative arterial disease the authors give pride of place to sympathectomy which they regard as the most valuable method of improving the blood supply, whilst recognizing that it in no way affects the progress of the disease and that the pain of claudication, the commonest symptom, is not relieved in more than 20% of cases. Widespread dissatisfaction with the results of sympathectomy has, however, given an impetus to the development of other methods such as the intra-arterial injection of vasodilators, and operations designed to restore the patency of the obliterated arteries. The authors state that they have not been impressed with the value of intra-arterial therapy and they do not favour disobliteration by removal of the intra-luminal clot. Whilst they concede that excision and grafting of the larger vessels, such as the aorta and iliacs, are usually successful, they consider that it can only be so in the smaller, more peripheral vessels when disease is minimal and localized.

It is inevitable that a textbook must lag behind the more recent developments of so

actively growing a branch of surgery as that of vessel grafting, and little information will be found in this book on the use of synthetic materials. However, the advantages of these are so many and the results of grafts fashioned from them so excellent that they seem destined to supplant almost entirely the use of homografts.

It is no reflection on the merits of this comprehensive work that in the matter of treatment it reflects the conservatism and scepticism which has always characterized the British reception of ideas which mostly originated abroad and often sprang more or less directly from the fecund imagination of René Leriche. The interested reader will be grateful for this statement of the personal experience and opinions of the authors, based upon the practice of the Postgraduate Medical School of London whilst the list of references at the end of each chapter will make it easy for those who wish to consider these opinions in their relation to the large accumulation of European and American evidence.

Medical Problems of Old Age. By A. N. Exton-Smith, M.A., M.D., M.R.C.P. (Pp. 344; 17 illustrations. 30s.) Bristol: John Wright & Sons Ltd. 1955.

"Medical Problems of Old Age" by Exton-Smith is the first textbook on the subject of diseases of old age to be written in this country and should prove most useful to general practitioners and also as an introduction to the subject for medical students and others who are interested.

It is well written, well produced and comprehensive in approach without being too detailed in text. It sets out primarily to describe the problems of illness in old age and to draw attention to the difference and variations of conditions found in old people.

The subject is well introduced in the earlier chapters "Clinical Implications of Ageing", "Principles of Diagnosis in the Aged", "Maintenance of Health". The author does well to set out some of the characteristics of disease and to draw attention to the multiplicity of pathology so frequently found in sick old people.

Under the heading "Common Symptoms" reference is made to many of the complaints of the old and attention is drawn to clinical variations which if not recognized may lead to mis-diagnosis. The author is to be congratulated on stressing the need to consider not only the primary illness with which the patient presents himself, but also the other disabilities found during full clinical examination.

"Practical Considerations in Home Care" collates many of the findings already reported and in so doing emphasizes, in an interesting section, the need for active prevention of disease and accident and for good medical care in the home.

Although short the chapters on "Some Problems in Medical and Nursing Care" and on "Surgery and Anæsthesia in Old Age" draw the reader's attention to these subjects, which must be under constant consideration in any geriatric practice, whether at home or in hospital.

In the chapter on principles of rehabilitation the author manages to touch on many essentials which must be appreciated by the clinician if he wishes to do good work.

As the author has included the rehabilitation of the patient with hemiplegia for special consideration and as it is one of so great importance in the elderly, greater detail should be given to the physical aspects.

The final chapter on mental disorders is most appropriate and helpful in such a book.

Current Therapy 1956. Latest Approved Methods of Treatment for the Practising Physician. Edited by Howard F. Conn, M.D. (Pp. xxx + 632. 77s.) Philadelphia and London: W. B. Saunders Company. 1956.

The arrangement and basic plan of this book on Current Therapy is similar to that of the earlier editions but, thanks to the editorial system by which the contributors to individual sections are varied, the descriptions of many of the treatments have a new look, as well as new material.

The text is as up to date as the inevitable time lag between submission of the typescript and publication permits.

Once again the subject matter is not confined to the relief of medical disorders, but encompasses dermatology, psychiatry and some gynæcological and obstetrical conditions, and diseases of the urogenital tract. The Editor is assisted by a panel of twelve consulting editors, and the text is written by close on 300 contributors, and an enormous amount of work has been put into it.

The value of any treatise on treatment is only really discovered by frequent reference to it in actual practice, and this book stands up to this test extremely well. Its considerable bulk is inevitable, as is the use of the names of American proprietary preparations, but these disadvantages in no sense outweigh its considerable usefulness.

This eighth annual edition is well up to the high standard of its predecessors.

Section of Psychiatry

President—W. D. Nicol, M.B., F.R.C.P.

[*March* 13, 1956]

DISCUSSION ON COMMUNITY CARE OF THE FEEBLEMINDED

[*Abridged*]

Dr. L. T. Hilliard (Physician Superintendent, Fountain Hospital):

Community care in relation to the feebleminded is usually contrasted with institutional care, but the terms are not mutually exclusive. Community care may mean that a mental deficiency hospital is responsible for defectives while they are working in the community on daily licence or while licensed to resident employment. Alternatively it may refer to the defective being cared for in the community by some other agency. There are some 50,000 defectives under statutory supervision by local authorities who may also receive help from other social agencies.

Such services are training and rehabilitation; the disabled persons register; probation officers and moral welfare workers; homes for unmarried mothers and National Assistance. These welfare services can be used to help defectives even when they have been certified as such, but it would be better to use the normal welfare services first and only deal with the mentally subnormal and socially inadequate person under the M.D. Act when these other agencies have failed.

Lilian's parents were missionaries in China. She was very nervous and backward at school and very poor at arithmetic but she could read fluently and had a good vocabulary. She led a very sheltered life in China from 1898 to 1939 and was treated as an incompetent person. She was never allowed to do things for herself or learn by experience so that when her parents died and she had to return to England she appeared to be feebleminded although her Wechsler I.Q. was 102 and Raven 95. When her brother was no longer able to look after her in 1952 she was certified as feebleminded at the age of 54 and sent to an M.D. institution. After her transfer to the South Side Home she was licensed to the care of a suitable landlady at the seaside, and discharged from the M.D. Act. She was then able to claim National Assistance being unable to work to maintain herself and this provided for her lodging and pocket money. Lilian has for the past two and a half years lived quietly as a retired lady who is now 60, without the doubtful benefit of being certified as feebleminded.

The mental deficiency services in this country, as at present administered under the M.D. Act, do not always give to the person being detained the maximum help and opportunity from which he could benefit. This view is supported by the considerable volume of evidence submitted to the Royal Commission on the Law relating to Mental Deficiency. The trouble is due in part to the M.D. Act being over forty years old. It was designed to deal with the problems of the mentally defective in the social circumstances of this country before the First World War. The M.D. literature of that period expresses the alarm which responsible persons felt at the thought of mental defectives multiplying and causing what was called race deterioration. It seemed then to be a world of paupers, workhouses, crime, prostitution, illegitimate children and gin. And the cause of all these social evils was believed to be the mental defective.

Henderson in 1902 in his study of the Dependent Defective and Delinquent Classes and their Social Treatment states: "An instructed public judgment will demand and provide for educational and custodial establishments for all the feebleminded whose presence in families and communities is a perpetual source of danger and injury. The unfortunate and helpless persons of this character who are at present kept in jails, county poorhouses, or left to wander about as the butt of ridicule and thoughtless sport, or the victims of lust, will be provided with permanent homes in isolated agricultural colonies, held in gentle and safe custody, enabled to produce their own food, and so to live happy and contented lives, without becoming the irresponsible progenitors of a miserable posterity."

The detention and custodial care of the certified defective thus became the primary aim of the M.D. institutions. Having failed socially the feebleminded had to be segregated

to prevent their further failure in the community and also to prevent them propagating their kind. The social evils were taken as the evidence of the mental defect. Allowance was seldom made for the environment in which the individual was reared. Malnutrition, inadequate education, lack of employment, poverty and overcrowding would contribute to the individual's social inefficiency but the resulting failure was not necessarily due to an arrested or incomplete development of the mind as defined in the M.D. Act.

To-day the social situation and the appraisal of the nature and cause of mental deficiency are very different, but the framework of the Mental Deficiency Act is unchanged.

There are now some 60,000 certified defectives in M.D. hospitals and the majority of these persons are of feebleminded grade. Many of them have been in institutions for a considerable period and it is usually considered that these institutionalized patients could not manage in the outside world. My experience with such cases has not confirmed this opinion and many of the patients who have been transferred to the Fountain and South Side during the past ten years from other hospitals, where they had not been tried on licence, have done well in outside employment. For example:

Ivy, as a child lived with her mother, sister and three stepbrothers in one room. Ivy had to sleep on the floor. She failed to progress at school and attended a special M.D. school. She now thinks the teaching there was inadequate, as she afterwards taught herself to read and write. When she left the special school she was certified as feebleminded. At the age of 15 she was sent to an M.D. institution. At 21 she ran away and obtained a job which she kept for a year until the police caught her and she was returned to the institution. After twenty years of further detention she was transferred to the Fountain Hospital in 1945. Her Binet I.Q. was 67 and her mild hypochondria improved after an ovarian cyst was removed. She was found resident employment on licence as a hospital domestic at £5 per week and was later discharged from the M.D. Act. She married and ran her home successfully, in spite of having been isolated from the world for the previous thirty years. No longer being able to have children of her own she and her husband obtained the approval of the local authority to act as foster parents. A little boy who would otherwise have had to be brought up in an institution is making excellent progress in her care.

If Ivy could have been sent at the age of 15 to a suitable hostel and given a job under supervision she might have avoided thirty years' detention as a mental defective. Alternatively had she been allowed to keep the job she held for a year when she ran away at 21 she might have been rehabilitated very much sooner.

The Fountain is primarily a hospital for mentally defective children but there are 80 beds for feebleminded women at the South Side Home at Streatham. During the ten-year period 1946–1955, 250 feebleminded women have been in my care. Of these, 152, i.e. 60% of all admissions, have been discharged from the M.D. Act. A further 40 are employed in the community on licence, 12 in residential jobs and 28 in daily employment. 6 have been placed under Guardianship. This means that of 250 consecutive feebleminded patients dealt with in this hospital under the M.D. Act more than 75% are living or working in the community.

In the case of women who are certified as mentally defective for the first time when adult, the commonest precipitating factor is an illegitimate pregnancy. The pregnancy itself is usually the main evidence of the patient being in need of care, supervision and control. Even when the patient is indeed limited in intelligence it is not always necessary to certify her for institutional care in such circumstances.

Ten patients were certified by the local authority and sent to South Side when they were already pregnant. These patients are now either back at home, in jobs or married. Most of these patients could have been dealt with at mother and baby homes for the unmarried if they had not been certified as mentally defective.

Patricia aged 26 was feebleminded and under statutory supervision. She lived at home and worked in a soda fountain. Her mother was a stewardess and so was away from home a good deal. Patricia became pregnant and was sent to the South Side Home as a place of safety under Section 15, where she was found to have Binet I.Q. 40, Wechsler 55, Raven 59. However, she was not certified for permanent detention because her mother was persuaded to change her work so that she could give her more supervision. Patricia went home with her baby when she left the maternity hospital and has been no further problem in the community during the past three and a half years.

An adult female patient working in the community on licence must not form attachments with the opposite sex. If a patient is kept in the community too long on licence such complications are the more likely to arise. A patient who becomes pregnant in such circumstances is at most hospitals recalled from licence, her child placed in a home and the patient deprived of any further chance of licence. A more liberal view may bring happier results if marriage is allowed. The experience of keeping her baby and looking after it may help the patient to mature and settle down.

Doreen aged 23 was on licence from South Side to her home in a south coast port. Unknown to her parents she became too friendly with a sailor and became pregnant. She was recommended for

discharge, was able to marry the sailor and is now living normally in her own home with her children. Her Wechsler I.Q. was 77 and on Raven's Matrices 79.

It is commonly stated that the children of certified feebleminded patients are in the majority of cases also of poor intelligence. There is no convincing evidence of this if allowance is made for the fact that the illegitimate child of a certified defective will have no normal home life, and being emotionally deprived by being brought up in institutions, may not make average progress at school. When he leaves the residential school for the educationally sub-normal (E.S.N.) he will have nowhere to go and he is very likely to be certified and sent to an M.D. institution, but this does not prove that the mental defect is hereditary.

If patients on licence in the community are given their discharge in a relatively short time they may make normal matrimonial arrangements and avoid illegitimate pregnancy. Of the 152 discharged patients 21 (14%) subsequently married.

Maisy at the age of 15 was charged with stealing a library book. She was certified under Section 8 of the M.D. Act and sent to the local institution for defectives. She absconded and was able to obtain employment and for some months lived in lodgings. She was in due course recaptured and later transferred to the Fountain Hospital. She seemed a very nice girl of normal education. Her I.Q. on the Wechsler was 96 and on Raven's Matrices 106 and she had a mature and stable personality. Three months after admission she was boarded out in a private house and soon after was found a residential domestic post in a large mansion. She was discharged from the M.D. Act. In due course she married the footman and they are now working very successfully as man and wife in a boys' school.

Maisy may have had a bad home and needed help and supervision as a child but one wonders why it was necessary to certify her as a mental defective.

One of the factors which has contributed to the high proportion of these patients being discharged is that I have often disagreed with those who certified them on the necessity to invoke the Mental Deficiency Act. If one thinks of them as mentally defective one is naturally pessimistic as to their ability to manage in the community. If one believes that medical, social or emotional factors are the main cause of their difficulties one is more likely to give them a chance in a different environment.

Wendy was certified as mentally defective at the age of 17 and transferred to the South Side Home three years later. She was undersized, had weakness and deformity in her limbs, and a childish and immature personality. She had had severe infantile paralysis at the age of 14 months and numerous orthopædic operations. She had spent most of her life in 19 different hospitals and institutions. Her mother had lost interest in her and did not even send a card on her 21st birthday. Wendy could write a letter normally, could find her way about and had a Wechsler I.Q. of 80, Raven's Matrices 80, Binet 81. If her abnormal childhood in institutions and her severe physical handicaps had made her appear mentally defective one might expect that a further period of seclusion from the world in a mental deficiency hospital would tend to make her more so. She was treated at South Side as mentally normal, encouraged to have an adult attitude to her disability and temporarily given work with normal staff in the needle room. She was then sent on licence to a Rehabilitation Centre and on her return was found sedentary employment in a factory on daily licence. She was visited and taken out to tea on her day off by two "Friends of the Fountain". This married couple very kindly agreed to help her and she is now living in their home on licence. A job, a normal environment, and her own achievements are helping her to mature and community care has replaced detention in an M.D. institution and she has recently been discharged from the M.D. Act.

A wide range of problems are dealt with under the heading of mental deficiency. Some of the patients in this series were not really mentally defective but circumstances had been against them. Inadequate efforts had been made previously to modify the environment of these patients so as to keep them in the community. Their previous social failure had been accepted at its face value and certification as mentally defective had followed almost automatically so that the patients became segregated from the community.

Life in an institution is not always the best preparation for life in the world outside. Long periods of segregation among mental defectives many of whom would be of considerably lower mental capacity than these patients, may produce either a dulling of the intellect and emotions or lead to rebellion, with disturbed behaviour and emotional instability. The most troublesome patients in an M.D. hospital are often those who are within the average range of intelligence and who justifiably feel that they are not in the most helpful surroundings.

These persons do best with the maximum opportunity for exercising, within their individual capacities, their powers of choice, judgment and self-restraint. Such patients should be encouraged rather than coerced and it is surprising how co-operative they will be if they feel they are being given a fair chance to take an active part in their own rehabilitation. Every patient at the South Side Home was on parole immediately on arrival even if she had been in a locked ward at the previous hospital. Patients were allowed to work outside as soon as a job was available, and if a patient found herself a job instead of waiting to be placed in

one she was always licensed to it, although it would be checked for suitability by the social worker. Small hostels would be of great assistance in the rehabilitation of such patients who have obtained daily work but have no homes.

Whatever their theoretical incapacity these certified feebleminded women, given the opportunity, were able to manage reasonably well in the community in spite of the considerable handicap of having been labelled mentally defective and isolated from normal life for considerable periods. It is submitted that in many cases a mental deficiency hospital administered under the existing M.D. law and regulations is not able to give the most appropriate help or rehabilitation for life in the community.

The development of new services for the welfare of citizens with special needs has had hardly any impact on the methods designed in 1913 for dealing with persons considered to be mentally defective.

In the past the medical staff of many mental deficiency institutions were concerned only with in-patient care. They had little contact with mentally subnormal persons in the community either before certification or after discharge. This may have accounted in part for their hesitancy to recommend licence and discharge from the institutions. Similarly the certifying doctors, not being attached to mental deficiency institutions had not first-hand knowledge of what happened to the patients they had certified or how they fared in the institutions.

Conditions are now changing and the combination of in-patient and out-patient work, which is taken for granted in every other department of hospital work, is beginning to be recognized as valuable also in mental deficiency practice. Out-patients departments attached to or staffed by M.D. hospitals, as for mental hospitals, should be the rule. By seeing all persons proposed for admission prior to accepting them in the Fountain Hospital or at South Side, I have found that a number can be kept in the community and the beds used for more urgent cases.

Admission without formality, usually for a temporary period, enables one to obtain the co-operation of the patient, remove her from the tensions that have developed at home or in her employment and give her a more favourable environment. At present the admission of adults to a mental deficiency hospital on a voluntary basis is not legally possible, there being no equivalent to the Mental Treatment Act of 1930, but temporary admission under Circular 5/52 has been used at South Side in some cases with good results.

When rehabilitation in the community seems likely within six months, small units are much more effective than large hospitals with as many as 2,000 beds. The South Side Home has had a high discharge rate partly because the patients admitted there felt they could cope with the environment and not be overwhelmed by it.

The finding of suitable jobs for patients who have been very unsettled, requires the co-operation of the Disablement Resettlement Officer (D.R.O.) in many cases, and more use should be made of Training and Rehabilitation courses.

The encouragement of persons willing to accept in their homes mentally subnormal individuals will increase the opportunities for community care of those already in institutions. It would also provide alternative accommodation for persons such as E.S.N. school leavers, who might otherwise be certified. The cost to the taxpayer of National Assistance for lodgings is considerably less than the cost of hospital care.

The strict regulations at present in force with regard to meeting members of the opposite sex should be considered on the merits of each case. It is unreasonable to expect individuals on licence who are only slightly subnormal mentally to maintain standards of behaviour very different from those of their associates in the community.

A patient certified under the Lunacy Act who escapes, is discharged by operation of law after two weeks in England or three in Scotland. A mental defective who absconds must remain at large until the current order expires, which may be up to five years. It would be fairer to let the Order lapse after a few weeks and, if the patient is subsequently discovered and found to need further institutional care, to make a new Order. This would ensure that a patient, who has by her own efforts begun her rehabilitation in a job, was not arbitrarily recaptured and returned to the institution without the need for institutional care being reassessed in the light of the new circumstances.

Many of the points made in this paper have been put forward by others in the evidence to the Royal Commission and are being increasingly accepted by psychiatrists in the mental deficiency service. There is still considerable confusion in the public mind and even more in the public press as to the working of the M.D. Act in practice. Instances have been reported where the certified defective seemed to have had an unnecessary curtailment of his liberty, and the efforts of his friends to liberate him appeared to have been resisted by all the power of authority. Some of these unfortunate instances have been taken to the High Court and

resulted in the legal vindication of the patient to the detriment of the reputation of the mental deficiency service. This paper is an attempt to present the other side of the picture.

Acknowledgments

I should like to express my appreciation to all those whose co-operation made possible the results summarized in this paper: To Sister Trinder who is in charge of the South Side Home, to Miss Kerry for the large amount of social work involved, to Mrs. Lydia Mundy for the psychological assessments and therapeutic interviews, to members of my Hospital Management Committee for their willingness to adopt a policy of early licence and discharge, to The Board of Control for their tolerance of my somewhat unorthodox procedure in difficult cases and, last but not least, to the patients themselves.

Dr. J. M. Crawford (Botleys Park Hospital, Chertsey, Surrey):

Use and Misuse of the Mental Deficiency Hospital

Although community care of mental defectives is usually associated with the feebleminded, bed accommodation is now so limited that we must think of it in connexion with all reasonably socially acceptable retarded people. At present a large proportion of the available beds is taken up by those patients least requiring all the amenities of the large mental deficiency hospital.

To illustrate this an assessment was made of the 97 patients admitted during the past five years from an urban population of 233,000. Of these, 44 may be expected to train to the level of competitive employment; 29 will always require some measure of support and, perhaps, mild medical supervision; 24 require prolonged nursing and medical care not easily, or properly, available at home or as out-patients.

The first point to emerge is that only 25% of the admissions are grossly physically and mentally handicapped. The other 75%, although deemed mentally defective, could conceivably be dealt with by other means elsewhere. It is suggested that mental deficiency hospital staff should combine with the general medical, educational, local authority and welfare services to deal, so far as possible, with these patients outside hospital and outwith the Mental Deficiency Act.

Especially in the case of children there is still almost a complete dichotomy between General Medicine and Mental Deficiency Practice. This can only be remedied by free interchange and linking up between all hospitals but, more especially at present, with pædiatric hospitals. This should then lead on to increased facilities for early diagnosis and to the setting up of what might be called a "Developmental Centre" where ANY physically and/or mentally defective child can be thoroughly investigated irrespective of whether or not he is "normal" or "mentally defective". This approach, so far only applied to spastics, is vital and such a centre is now urgently needed for investigation, treatment and research in this region.

The second point of importance in the admission figures is that 35 of the 44 "high-grade" patients might have been dealt with outside hospital by the provision of, first, male and female training units with ancillary hostel accommodation for those adults convicted of often mild antisocial behaviour and, secondly, more adequate residential special school accommodation. Too many children with intelligence quotients in the sixties are being excluded from the educational system to-day.

Amongst the 29 patients admitted who were definitely subnormal in intelligence and often subnormal in physique only 10, by reason of chronic physical disability, e.g. epilepsy, really justified care in a large, well-equipped hospital. By the placement, in strategic areas, of "Country house" establishments minimally staffed and equipped, a very large number of patients like this, whose home care has deteriorated or ceased, could be cared for. With only slight support and supervision they can minister to their own daily wants and, possibly, staff a sheltered workshop.

Alternative care has now been proposed for 54 of the 97 admissions. Of the 24 cases in the grossly defective group at least 6 might continue under home care if certain community facilities were provided or improved. These are: (1) better out-patient investigation, advice and treatment; (2) increased social work from both hospital and Local Health Authority level; (3) increased financial aid for parents; (4) increased occupation centre accommodation; (5) increased short-stay accommodation for times of household emergency and holidays.

In conclusion, if better diagnostic and alternative facilities came into being and mental deficiency practitioners could play their full part in conjunction with all other branches of medicine and the Social Services it might be possible to keep approximately 50% of the present type of admission in the community. In so doing not only would better use be made of the available beds but many young children now deemed ineducable and mentally defective might receive the comprehensive investigation and highly specialized treatment which is, at present, largely denied to them.

[*May* 8, 1956]

DISCUSSION: OBSESSIVE COMPULSIVE STATES

Dr. John Pollitt:

The Natural History of the Disorder—[Abridged]

Almost a hundred years have passed since the term "obsession" was first used by Morel (1861), but it is only four years ago that Dr. Desmond Curran (1952) pointed out our ignorance of the natural history of obsessive compulsive disorders.

Whilst working at St. George's Hospital I was able to find 150 patients with obsessional symptoms as the dominant feature. In this investigation, an obsessional symptom is defined as a recurrent or persistent idea, thought, image, feeling, impulse or movement which is accompanied by a sense of subjective compulsion and a desire to resist it; the event being recognized by the individual as foreign to his personality, and into the abnormality of which he has insight.

The differential diagnosis between obsessional illness proper and depression with obsessional features is often difficult. All doubtful cases were excluded, as were those who responded to E.C.T.

Of the 150 cases, 69 had been admitted to the psychiatric in-patient unit of St. George's, 81 were private patients of Dr. Curran. There is good reason to regard this group as representative of obsessional states since few are admitted to mental hospitals.

The data for this study was obtained from case records, but for the follow-up a special questionnaire was used and additional information came from out-patient notes, social workers' reports and from notes kindly sent by psychiatrists under whose care some patients eventually came. When possible, patients and their relatives were interviewed personally. A patient's fate was not assumed on the basis of his or her questionnaire reply alone.

According to the present series, the incidence of the obsessional illness is low. The males formed 2·8% of the hospital male admissions, females forming 4·2% of all female admissions. The incidence in the private series, both sexes together, was just over 1% of all cases. It is understandable that there should be a higher incidence in the hospital series, since the more severely ill patients and patients for leucotomy were admitted there.

The illness began, most commonly, in early life. Fig. 1 shows the distribution of patients

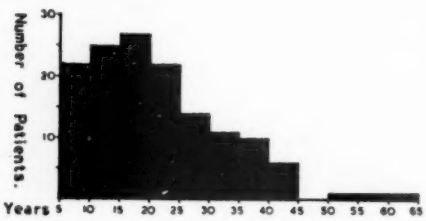

FIG. 1.—Frequency histogram showing the distribution of patients according to their age when their first symptoms developed.

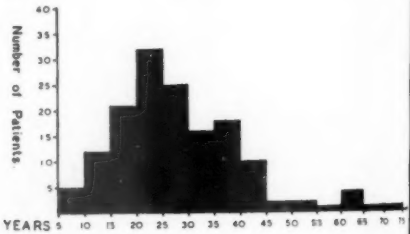

FIG. 2.—Frequency histogram showing the distribution of patients according to their age when the present illness began.

according to their age when the first symptoms, as distinct from the present illness, developed. 70% had their first symptoms before the age of 25 and only 4 of the 140 had their first symptoms after 45. As age increased, fewer and fewer had their first symptoms. Hence, it is unlikely that patients, experiencing these symptoms for the first time after the age of 45, are suffering from pure obsessional states and this finding of an early onset confirms the clinical impression that an illness beginning in later life, with obsessional features, is more likely to be primarily depressive.

Previous attacks of symptoms, sufficiently severe that medical advice was sought, were reported by 82 patients. The majority of the attacks occurred between 10 and 30 and lasted less than a year. Three-quarters of the patients had from one to three such attacks but only 10 had more than three. The average was two per patient.

Thus the phasic nature of the obsessional illness differs from the course of affective disorders in general in that the bouts tend to occur in childhood, adolescence and early adult life rather than later. Whereas obsessional symptoms seem to be relatively common about puberty, adolescence and early adult life, affective psychoses are rare before 20 (Mayer-

Gross, Slater and Roth, 1954). That such previous attacks, with a good prognosis, exist and that they occur in the early decades should be borne in mind when considering leucotomy as a treatment for younger people with obsessional illnesses.

Though it is often taught that any mental illness showing a phasic course is basically of depressive type, Bumke (1929) observed that the periodic occurrence of obsessional states was not a reason for including them in the manic-depressive group because periodicity is a function of the human psyche. Lewis (1936), Greenacre (1923), Ibor (1952), and Gordon (1926) also hold the view that the obsessional state is a phasic illness.

There was no simple relationship between the number of previous attacks and the ultimate prognosis and no correlation between the total duration of such attacks and the prognosis.

The present illness is taken as the unremitting train of obsessional symptoms for which the patient attended hospital or privately for medical advice. Fig. 2 shows the patients distributed according to their age when the present illness began. It can be seen that half the total number of patients began their illness in late adolescence or early adult life, between the ages of 16 and 30. Only 1 in 15 began after 45, that is about 7%. Greenacre (1923) confirms these findings and observes that obsessional states arise usually during the active striving period of life and only rarely in the later years.

At this point it is interesting to compare the relative expectation of developing an obsessional illness or a manic-depressive illness as age increases. The figures for manic-depressive patients are those given by Slater (1938). Table I shows this comparison.

TABLE I.—THE RELATIVE EXPECTATION OF DEVELOPING AN OBSESSIONAL OR MANIC-DEPRESSIVE ILLNESS AS AGE INCREASES

Age	Obsessional	Manic-depressive
20 years	25%	2% of the danger passed
30 ,,	63%	14% ,, ,, ,, ,,
40 ,,	85%	33% ,, ,, ,, ,,
50 ,,	93%	55% ,, ,, ,, ,,
60 ,,	96%	79% ,, ,, ,, ,,
70 ,,	98%	96% ,, ,, ,, ,,

TABLE II.—THE PRECIPITATING FACTORS OF THE ILLNESS IN 93 OBSESSIONAL AND 90 NON-OBSESSIONAL PATIENTS

Precipitating factors	Obsessional	Non-obsessional patients
Sexual	28	3
Betrothal .. } Family difficulties } Marital difficulties	15	39
Bereavement ..	14	2
Occupational ..	14	17
Physical	4	13
Pregnancy .. } Menopause .. } Puberty ..	11	9
Other factors ..	7	7

Precipitation of obsessional symptoms.—The events leading to the onset of the present illness were known in 93 of the cases reviewed.

These events were considered significant by both the patient and doctor and were elicited in the course of routine history taking. Table II shows the number of obsessional and non-obsessional patients in whose case these various precipitating circumstances operated. The control figures are shown in order to exclude as far as possible any bias due to psychological orientation. They are derived from cases admitted to hospital during the same period as the obsessional patients, and the two groups have similar age distributions.

The sexual factors included seduction, willing or unwilling perverted acts, witnessing sexual acts or perversions, dyspareunia and impotence. The figures are highly significant statistically. These overt sexual events appear to have a definite place in the initiation of symptoms in the obsessional disorders. The high figure for bereavement, which meant death of a near relative or friend, fiancé or child, is significant, also the low figure for physical precipitation in the obsessional series. Approximately half the obsessional illnesses were brought on by circumstances likely to produce intense emotion, demonstrating the reactive nature of their onset.

Obsessional patients are usually regarded as particularly able to withstand symptoms of various kinds and to carry on their lives in spite of suffering. In this investigation, the average patient endured obsessional symptoms in the present illness almost five years before becoming incapacitated by them. The criterion of incapacity was inability to carry out accustomed work or social duties which were a significant part of the patient's life.

Approximately half became disabled within a year, the remainder broke down only after a considerable period had elapsed from the beginning of the illness. About two-thirds broke down before they were 40; there were very few who broke down after 50.

The average length of time a patient suffered before attending for advice was seven and a half years. This high figure is due to the inclusion of relatively few cases who had long

histories. Evidently the obsessional patient can tolerate his symptoms comparatively well for a long time without specialist medical advice.

Qualitative observations on the course of the illness.—A variety of factors made the patient's symptoms worse. A recurrence of the situation which caused the commencement of the illness or any stimulus related to the content of the obsession was potent in causing a relapse, also any stimulus producing anxiety, such as an increase in social, occupational or sexual responsibility. A few patients were specific in their reactions, they underwent considerable mental and bodily stress during remissions without relapsing, yet recrudescence occurred when the specific stimulus came along. These patients recount variations in their symptoms due to such a variety of circumstances that the reactive nature of the obsessional state must be accepted.

Probably the greatest factor bringing relief from symptoms was a lessening of anxiety, whether produced by removal from a distressing environment, reassurance, superficial psychotherapy, sedatives or leucotomy. Many improved when their responsibilities were lessened, for example when they were admitted to hospital.

Follow-up.—Much is known and emphasized in teaching, about the way in which obsessional symptoms increase and spread. Much less is known about the recovering obsessional and this may be because the patient stays away from his doctor at this time, lest he be reminded of his symptoms which he had such difficulty in forgetting during his illness.

It was not possible to follow-up all patients. Nevertheless, there was sufficient evidence of the course of the illness in 98 cases. The follow-up period from the time of being first interviewed was from three months to fifteen years. Each patient's condition at the end of the follow-up period was assessed and five categories were recognized in a classification similar to that used by Müller (1953). The five categories are:

Group 1: The patients who are socially adapted and free of symptoms.
Group 2: Those who are socially adapted but still experiencing mild symptoms.
Group 3: Those whose symptoms have improved but who are poorly adapted socially.
Group 4: Those whose symptoms are as severe as or worse than when they were first seen.
Group 5: Those whose obsessional symptoms were replaced by others of a different kind.

In the last group, one female developed a frank schizophrenic illness; this was the only case. Two patients died, one from carcinomatosis, the other committed suicide during a depressive illness, four years after leucotomy.

Table III shows the fate of the 98 patients in categories 1 to 4. If we ignore the period of

TABLE III.—THE DISTRIBUTION OF PATIENTS IN THE FOLLOW-UP CATEGORIES

(1) *At Termination of Follow-up Period.*

Categories	1	2	3	4	Total patients
All patients	31	30	15	22	98
Leucotomized	15	6	7	5	33
Non-leucotomized	16	24	8	17	65

(2) *After Four Years or More Follow-up.*

Categories	1	2	3	4	Total patients
All patients	16	13	7	8	44
Leucotomized	4	4	4	3	15
Non-leucotomized	12	9	3	5	29

follow-up for the time being, we find that, at some stage or other, one-third of the patients reach a stage of social adaptation and a further third become free of symptoms (Table III (1)). Roughly one-half of those who recovered had previously shown compulsive motor phenomena. The patients who did not suffer motor compulsions recovered in a mean period of five years from the beginning of the illness, but those who had motor compulsions took seven years on an average.

As the illness has a phasic course, it is desirable to have a longer period of follow-up to allow for relapses. If this is done, and four or more years of follow-up are taken (Table III (2)), the sample contains many fewer cases due to the exclusion of those who were followed only for a short time. Accepting the smaller figures, there is a preponderance of patients who did well compared to those that did badly.

Results.—The results of the present investigation are more favourable than those given by other workers such as Lewis (1936), Müller (1953), and Rüdin (1953) but the shorter period of follow-up in the present series may be responsible. In the present study, two-thirds of the patients followed-up made very good progress. In the light of this evidence, the obsessional state has a much better outcome than is usually thought and it seems justifiable to view the prognosis, in many cases, with optimism.

Recovery took place frequently in the early years of the illness and much less commonly

when the illness had lasted several years. Many patients with comparatively short histories recovered but only a few who had suffered for a number of years did so. 37 of the 61 patients known to have recovered or become socially adapted, reached this stage in the first 5 years of their illness. Only 5 of the total number who recovered had been ill for more than 20 years. The prognosis of the obsessional state would appear to be related to the time a patient has already suffered in the present illness. The process of recovery is active in the early years of the illness and it is reasonable to suppose that therapeutic aid is then most valuable. There is also a relationship between the prognosis and the length of time a patient has his symptoms before seeking advice. Those who improved little or were worse had been ill for longer periods than those that recovered.

The mode of recovery in these patients was almost invariably gradual; the symptoms became less and less troublesome until they were unobtrusive.

Prognosis.—The elements of a good prognosis should be shown by those who recovered or improved considerably. In fact they were seen much earlier in the development of the illness than those who had leucotomy. In many cases those that showed a good prognosis had not had previous treatment during the present illness. The mean age of recovery in 31 patients was less than 40 years. The average age when the illness began was the same in those that did well as in those that fared badly. Those who recovered had experienced fewer attacks than the rest of the series.

The only clear-cut prognostic criterion seems to be the time for which an individual has already suffered in the present illness. Environmental factors play a big part and these are almost impossible to assess.

If all our patients were obsessionals, there would be little need for mental hospitals. Enquiries at two mental hospitals, which have together 2,550 beds, showed that only 4 of the patients resident were diagnosed as obsessional states and 2 of these were males who had been sufficiently ill to require leucotomy. 4 hospital cases are known to have become voluntary patients subsequently, none were at any time certified.

Summary.—The illness usually began in the first half of life and rarely after 45. Previous episodes of symptoms were common in early life and in those patients who had these episodes, two was the average number, per patient, and they usually lasted a year or less. Obsessional symptoms started fairly frequently before the age of 20, they were often precipitated by extreme emotion. The severity of the established symptoms was directly affected by environmental changes. Two-thirds of the patients followed-up improved very much or were relieved of obsessional symptoms in one to eight years.

Several points arise which may be of value in the management of patients. One indication for optimism is the young patient, seen soon after the beginning of his symptoms, who has not been treated before. Excitatory treatment such as E.C.T. or abreaction seems best avoided and the importance of reducing anxiety early in the illness should be stressed. Regarding leucotomy, a young patient and a short illness demand the greatest caution.

It is hoped that the present conclusions will be of some value as a yardstick against which the profound effects of modern treatments on the obsessional state may be judged As wrote Fuller (1642), over 300 years ago, "Without history a man's soul is purblind, seeing only the things which almost touch his eyes".

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Dr. John Pippard (Claybury Hospital, Woodford Bridge, Essex):

The Surgical Treatment of Obsessional States [*Abridged*]

In 1950, Sargant and Slater discussed the results of leucotomy in about 40 cases of obsessional illness, and have since amplified their views (1954). They find that modified cuts may be sufficient and that the best results are obtained in patients with well-adjusted premorbid personalities whose symptoms begin in the third or fourth decade rather than earlier; who show responsiveness to the environment, a tendency to reactive anxiety, and anxiety and tension in association with ruminations and phobias rather than an abundance of "motor" symptoms. Results are less good in rigid and anergic individuals and particularly in those who complacently accept their symptoms. Schizophrenic symptoms, abnormal sex behaviour and aggressiveness are regarded as contra-indications.

Partridge (1950) described the results of standard prefrontal leucotomy in 24 patients operated on essentially for obsessional symptoms. Of 23 survivors 11 became virtually free of symptoms and the rest showed varying degrees of improvement. The differences between those who became symptom free and the rest could not satisfactorily be accounted for by the length of time over which symptoms had been shown, nor by their severity, nor by the psychodynamics; "the only decisive factor that could be discerned was the entrenchment and standardization of the rituals . . . where there was variability there was hope". In addition the "general rule [holds] that the better the personality the more satisfactory, on the whole, is the operative outcome".

Freeman and Watts (1950) also stress the importance of energy-drive in favouring satisfactory reorganization of the individual after operation. Unfortunately their book gives little detailed information about their 85 obsessional cases; the results of standard leucotomy in the "obsessive tension states" are almost the same as in the "obsessive-compulsive neuroses" (about 55% "good" and 35% "fair"). They consider that leucotomy reduces or abolishes the feeling tone attached to the ideas; these continue and the compulsions often last for a long time, but the conflict is no longer present; "it would appear that their persistence is a matter of habitual reaction". Three and a half years after rostral leucotomy a patient writes: "I continue to have odd obsessions like always crossing the road at the same spot, avoiding certain gratings and paving stones and counting, mentally, to many things I do. I even, after having laid out my clothes in a particular and precise manner, follow a little ritual of counting when I get into bed at night; these odd things . . . have become habits. They give me more comfort than distress and anyway to attempt to stop them would be unthinkable."

Worth-while relief can be obtained with a variety of modified techniques in more than half the cases. Standard leucotomy should rarely be done except, perhaps, occasionally as a second operation. Le Beau (1953) favours anterior cingulectomy for the relief of obsessions but the 7 cases he describes do not convincingly support cingulectomy rather than the other frontal operations he performed. Whitty (1955) reported great improvement in 6 of 7 mainly obsessional patients followed up for more than a year after cingulectomy. Busch *et al.* (1955) report good results in 5 of 6 obsessionals who had an orbitomedial undercutting by Scoville's technique. Moore (1951) had only 3 failures from transorbital leucotomy in 19 psychoneurotic patients (mainly obsessional and anxiety-tension-phobic states).

Sperling and Boroffka (1954) carried out a variety of leucotomies, mainly transorbital and standard, in 26 severe obsessionals. They classify the cases into: (1) Obsessional neurosis, where the main causative factor appears to be conflict in the face of environmental stress; (2) Obsessional illness (Zwangskrankheit), where severe symptoms which cannot be clearly understood appear early in life in otherwise normal personalities; (3) Psychopathy with anankastic traits in which obsessions occur only as part of the symptomatology of very disturbed personalities; and (4) Senile obsessions. 11 of 14 cases of Zwangskrankheit were lastingly improved, 6 of them by transorbital leucotomy alone, but their conclusion that leucotomy is of value only in this group is not justified by the figures: only 3 cases were classified as obsessional neurosis; it could well have been by chance that none of these was lastingly helped. I have found good results in cases of "obsessional neurosis".

Follow-up.—Rostral leucotomy (McKissock, 1951) was done in 30 cases in which obsessional symptoms were the dominant feature; these form part of a larger series operated on by Mr. McKissock between 1949 and 1952 which I personally followed up (Pippard, 1955). Continued personal study has not been possible but during March 1956 I wrote to these patients and some up-to-date information is available in 21 of the 30 cases. The original follow-up covered a post-operative period of one and a half to four years; recent information brings this to between three and a half and five and a half years and, in one case, seven years. In general, improvements following operation and recorded two years ago have been consolidated rather than lost; in many cases obsessional activity has continued to fade into the

background, confirming Freeman's observation that the process of recovery may be long. No marked change has been reported by any patient who had not originally been much helped by the operation. 2 patients have married happily since I saw them; this would have been unthinkable before operation. Another married unhappily and had a temporary return of symptoms needing treatment in hospital.

At the time of operation the patients were between 24 and 62 years old; age alone did not appear to be significant for the result, nor did duration of illness, for good results were obtained in illnesses of from two to twenty-five years' duration and poor results in those which had lasted between one and twenty-three years.

Table I relates the age at which the first obsessional symptoms occurred to the operative

TABLE I.—RELATING AGE AT ONSET WITH OPERATIVE RESULT

Age at onset of first obsessional symptoms	Result of rostral leucotomy		
	Good	Fair	Poor
0– 9	3	—	3
10–19	5	1	5
20–29	3	1	3
30–39	3	2	—
40–49	1	—	—
Total	15	4	11

result. This was good or fair in 9/17 which began before the age of 20 and in 10/13 whose first symptoms occurred later. The difference is not significant but agrees with the views of Sargant and Slater.

The personality setting was more important than age of onset, with good results in several, not markedly immature or inadequate, whose illness began in childhood or adolescence. It is generally held that the better the premorbid personality, the better, on the whole, are the results of leucotomy. 12 patients, before illness, had some obsessional personality traits, such as obstinacy, excessive orderliness, preoccupation with cleanliness, &c., and these were marked in 5 cases. 7 patients (including 3 of those with obsessional traits) had essentially adequate personalities and had been reasonably well-adjusted citizens. 13 had markedly immature personalities; they were, on the whole, timid, anxious, lonely and dependent; several were very inadequate and many had had lifelong neurotic symptoms. The remaining three patients do not fit readily into any of these groups. Only one patient could fairly be described as anergic and operation made little difference to her.

"Rigidity" is a term often used impressionistically and without precise definition in clinical descriptions of personality; it conveys the idea that behaviour is governed by strict rules (whether or not these are consciously recognized) and that attitudes are slow to alter in response to situational changes. Some degree of rigidity in this sense is, of course, a feature of obsessional personalities, but in this series marked rigidity was unusual and a really severe degree was apparent in only one case, a haughty, emotionally cold schizoid man. In this case the result was poor, but I would hesitate to say that the prognosis is necessarily bad in "rigid" personalities; certainly there is not likely to be much change in their personalities from rostral leucotomy, but rigid individuals may have found a satisfactory way of life before illness incapacitated them and may do so again if symptoms are relieved by operation.

Table II relates the results of leucotomy to the premorbid personality characteristics; it

TABLE II.—RESULTS OF ROSTRAL LEUCOTOMY RELATED TO PERSONALITY

	Total	Good	Fair	Poor
Obsessional traits present	12	7	1	4
"Adequate" personalities	7	7	—	—
"Inadequate", neurotic personalities	13	3	3	7
Others	3	1	—	2

TABLE III.—RESULT OF ROSTRAL LEUCOTOMY IN "MOTOR" AND "SENSORY" GROUPS

Type of obsessional symptoms	Good	Fair	Poor
Mainly thoughts: phobias, ruminations, doubts, &c.	5	2	4
In addition, much compulsive motor activity	10	2	7

is striking that all 7 of the patients with "adequate" personalities did well, but only 3 of the 13 "inadequates".

Prognosis.—I have been unable to devise any tabulation relating symptoms to results which is not positively misleading; the form the symptoms take is of little help as a guide to prognosis, with one exception; the well-recognized intractability of long-ingrained habits of behaviour is shown in this series; 3 patients had pursued for more than twenty years

elaborate cleaning and decontaminating rituals which had varied little except to grow more incapacitating. None did well or lost their rituals. In a fourth case it was unfortunately not realized before operation that she was using obsessional symptoms hysterically to punish her husband; leucotomy diminished her energy, to her great annoyance, because she could not accomplish so much in the time, but she overcame this to some extent by making her husband do a good deal of the obsessional cleaning, until in desperation he left her.

11 of the other 26 patients were troubled mainly by obsessional thoughts: phobias, ruminations, doubts, obsessing words and so on. The remaining 15 had, as well, much compulsive motor activity. More than half the patients were depressed to some extent, some of them severely, and all were tormented by their fears, doubts or compulsions. Table III shows no significant difference between the results in the predominantly "motor" and predominantly "sensory" groups; leaving out the cases with long-lasting, relatively invariable ritualistic behaviour there are only 3 poor results in the "motor" group. The reasons for this seem to be more in the personalities than in the type of symptoms; 2 of the failures were the most pathetically immature and inadequate people in the whole series and the third was a psychopath with symptoms from childhood. Similar considerations apply to those whose symptoms were mainly sensory; in 3 of the 11 the onset of illness was directly related to a conflict situation, e.g. a 43-year-old man who nine years previously had been upset when his wife told him that she had allowed a man to kiss her; his thoughts gradually condensed into a repetitive "he kissed her, don't be silly of course he didn't, he kissed her . . .", and later to a single endlessly repeated swear word. His distress was relieved by leucotomy and the obsessing thoughts faded almost to insignificance. In each of these 3 cases the result was good, but their personalities were better than those of the rest of the group, and this may possibly have been of greater importance in determining the good results than the nature of the symptoms or manner of onset.

It remains to consider the social setting within which these obsessional illnesses have occurred. Dr. Pollitt has concluded that anything which relieves anxiety is helpful to obsessionals; this is no less true after leucotomy than it was before. After operation a patient *may* be better able to go back to cope with an anxiety-provoking situation, but he is much more likely to remain well if he can be shielded from the type of situation to which he is "sensitive". At least 2 good results in inadequate people seemed partly due to altered circumstances in their lives which allowed the obsessional process to fade out instead of keeping it active by constantly stimulating anxiety. For example, an immature 25-year-old typist, daughter of a jealous neurotic mother, developed hypochondriacal fears during adolescence which greatly increased when her mother told her that she had had a baby before marriage when a man "just touched" her. At 23 her employer exposed himself to her, she ruminated on the possibility of having a baby and began to wash compulsively. After leucotomy she lived and worked away from home; obsessional thoughts still occur at times, particularly if she visits home, but are less than ever before. There is little doubt that leaving home was an important factor in her improvement. She, like several others in the series, has gone on having some psychotherapeutic support, and greatly values it, but she sees her therapist only infrequently now. Another patient had had weekly sessions for seven years before operation, but now needs only two or three a year.

Some of the least satisfactory results have been in anxious immature patients returned after operation to the very circumstances in which they fell ill; it is useless to leucotomize the inadequate individual, overwhelmed by circumstances, unless some way can be found to lighten the burden. In one case, rostral leucotomy failed and eighteen months later a unilateral standard operation was done; after this she left hospital to go to a new home with her husband, away from the family tension which had apparently been too much for her. She has made a remarkably good recovery, in which both the factors of an adequate leucotomy and relief of the stress to which she had been subjected were important. In other cases, where patients have been driven by circumstances to break established habits, they have experienced less distress than they expected and have gone on to consolidate their gains.

Summary.—In assessing the suitability of any case for leucotomy it is necessary to consider not only the symptomatology and the personality of the patient, but both of these in relation to the environmental difficulties likely to be experienced after operation.

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Dr. E. Stengel (Institute of Psychiatry, London):

In trying to study the natural history of a mental disorder, i.e. its course uninfluenced by therapeutic intervention, we are in a difficult position nowadays. It cannot be said that Dr. Pollitt's patients received no treatment. In comparing different samples of cases we usually compare groups of patients who were subjected to different kinds of treatments, whereby the variables are often multiplied by the fact that many patients had several kinds of treatments. Dr. Pollitt has found only one schizophrenic development among 150 obsessionals, while Müller of Zurich found that out of 57 obsessionals, 7 had developed schizophrenia after twenty-five years. Dr. Pollitt is probably right in attributing this discrepancy to the difference in the periods covered by the two follow-ups, but this may not be the only reason. If we accept the evidence of the workers at Yale, we should expect a lower incidence of schizophrenia in a group such as that of Dr. Pollitt's which has a large proportion of middle and upper class subjects, than in one composed entirely of patients from a public mental hospital such as Müller's.

Dr. Pollitt's observations about the length of time the patients suffered before attending for advice are particularly interesting. Dr. Ismond Rosen, working at Bethlem-Maudsley Hospital, found that most of the obsessionals who developed schizophrenia had come to the attention of the psychiatrist only as the result of their schizophrenic symptoms. Obsessionals seem more anxious to cope without psychiatric help than other neurotics and they are rather secretive about their symptoms. Dr. Pollitt's observations about the precipitating factors are of great interest. His broad generalization that any stimulus likely to produce anxiety is apt to make the patient worse, and vice-versa, is in keeping with the findings of psychoanalysts who have always emphasized the fundamental role of anxiety in obsessional neurosis.

The only prognostic criterion which Dr. Pollitt has found reliable, i.e. the length of time the symptoms had been in continuous existence, has not, surprisingly, proved a guide in the prediction of the result of leucotomy. The most striking among Dr. Pippard's findings is the correlation between the effect of the operation and the personality feature of rigidity. It seems that he has adopted a more limited concept of rigidity than most psychiatrists. It is usually taken for granted that every obsessional neurotic must have a rigid personality, but Dr. Pippard has made it clear that he does not hold this view. He appears to refer to lack of social adaptability, which Partridge has found prognostically ominous, perhaps associated with affective rigidity. The main criterion of the rigid personality as it is generally understood, is its unmodifiable dependence on strict codes of behaviour and its lack of resilience in changing circumstances. Dr. Pippard's studies will prove of considerable value for those psychiatrists who have to consider the indications for leucotomy.

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Reserpine: Problems Associated with the Use of a So-called "Tranquillizing Agent"

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RESERPINE is one of the two most prominent representatives of that group of substances which have come to be widely known as the "tranquillizing agents". I shall try to review briefly what has been learnt about this drug, to summarize our own experience with it, and to indicate some of the important deficiencies in our knowledge, specifically about reserpine but by extension about its congeners.

So far the mode of action of the drug is not clear and questions as important as its absorption, its distribution and fate within the body, and the long latent period before its action are still unanswered.

The property of the drug which has aroused the interest of most neuropsychiatrists and which is chiefly responsible for its reputation in the treatment of mental disorders consists

in a supposedly distinctive sedative action. This differs from the condition associated with barbiturate administration in that while motor activity is subdued, sleep is not induced and the electroencephalographic patterns of sleep are not recorded; further, with human subjects relief from the distressing emotions associated with states of anxiety, agitation and tension has also been claimed. It is to such a complex cluster of phenomena that the term "tranquillization" has been applied. According to the Oxford English Dictionary the adjective "tranquil" is defined as "free from agitation or disturbance".

In the past three years the epithet "tranquillizing" has been vigorously applied to a number of pharmacologically diverse substances. The word is without scientific meaning and should not be employed as a nominal substitute for an understanding of the mode of action of the drug concerned. The need for this knowledge remains unsatisfied whether the drugs be called "tranquillizers", "ataraxics", "deturmoilizers" or "apatheticatory agents".

It is none the less easier to discard the term "tranquillization" than to replace it. Little progress in this direction has been made so far by the many laboratory studies on reserpine. Its actions on the nervous system extend beyond those described to account for its cardiovascular effects and, depending on the investigators' technique, reports have appeared of its action on the limbic system (MacLean *et al.*, 1956), on the mid-brain reticular substance (Rinaldi and Himwich, 1955), on conditioned reflex responses (Gliedmann and Gantt, 1956), and on cerebral synaptic transmission (Langfitt *et al.*, 1956). Ingenious biochemical speculations have assigned to reserpine a role as liberator of 5-hydroxytryptamine from binding-sites in the body and brain (Kuntzman *et al.*, 1956). It must be emphasized, however, that even if these physico-chemical reactions should be confirmed and elaborated they will remain incomplete without more knowledge of the complementary psychological changes which go with the response to reserpine. Interest in psycho-pharmacology has been reawakened among psychologists in recent years by the carefully controlled operant conditioning techniques associated with the work and views of Skinner (1953). The chief problems set by these behavioural studies is that of relevance; the effects of reserpine on the pecking responses of pigeons, for example, can be accurately described and repeated but they are difficult to relate to the changes in behaviour brought about in schizophrenic patients. By contrast, the highly relevant modification of human behaviour and experience by pharmacological agents acting on the central nervous system has been systematically studied by very few workers, all of whom agree that the effects produced by these drugs in therapeutic doses depend in part on the personality of the subject and the circumstances of administration as well as on the physical properties of the drugs (von Felsinger *et al.*, 1955). Very little work of this type has been carried out with reserpine.

In these circumstances reserpine therefore presents a familiar problem to the clinical psychiatrist: namely, that of assessing the efficacy of a therapeutic agent about which too little knowledge has been accumulated, in the treatment of conditions whose ætiology and natural history are for the most part imperfectly understood. When we began using reserpine at the Maudsley Hospital less than two years ago there were very few reliable accounts of its use in the treatment of neuropsychiatric conditions and almost no controlled clinical studies. Dr. D. L. Davies and I therefore conducted a clinical trial on a mixed group of out-patients, the majority of whom were suffering from anxiety and depressive reactions. The patients were given either reserpine, prescribed as Serpasil in a dose of 0·5 mg. by mouth twice daily, or a seemingly identical placebo, for a period of six weeks. The two substances were allotted by the hospital pharmacist who employed a random method and alone knew the nature of the drug dispensed to each patient; the usual crop of placebo reactions which was observed during the weekly examinations quickly demonstrated the importance of such precautions in testing patients of this type. At the end of the sixth week the response of each patient was estimated by rating scales which were completed by doctors and patients. The results demonstrated a clear-cut difference in favour of those patients treated with reserpine but it was not possible in a clinical trial of this type to determine which factors would enable the clinician to select or reject individual patients or classes of patients for treatment (Davies and Shepherd, 1955).

An attempt was made to examine the efficacy of the drug in the treatment of a more homogeneous group, a small number of middle-aged males who presented an indisputable picture of involutional depression and who were reasonably expected to respond to a course of E.C.T. In the treatment of these cases any benefits of drug therapy could be measured against those predicted of a well-tried alternative procedure. The dose employed for these patients was much higher, between 10 and 15 mg. daily and was prescribed for three weeks, the period of time during which E.C.T. would otherwise have been administered. No clinical improvement was observed on reserpine; after a further week without treatment the patients were started on E.C.T.; all of them recovered after three weeks of this treatment. The value of the drug in the management of major depressive illness thus appeared dubious;

this impression has since been strengthened by the results of Dr. Felix Post's carefully conducted trial of reserpine in the treatment of affective disorders arising in the senium.

The early claims made for reserpine rested on its use in the treatment of chronic mental illness. While the effects of reserpine on a disturbed patient population were being studied at Netherne Hospital, Dr. David Watt and I studied the response to medication of a group of schizophrenics who had resisted all previous treatment and had remained inactive and apathetic for many years (Shepherd and Watt, 1956). 24 such patients could be found at St. John's Hospital, Buckingham hire; all were female, with a mean age of 40·5 years and a mean hospital stay of 15·8 years. The prognosis was regarded as very poor in every case and a comparison of the effects of reserpine and chlorpromazine on the group was undertaken. The patients were allotted by a random method to three sub-groups of 8; a latin square design ensured that each sub-group received reserpine, chlorpromazine, and a placebo over three separate periods of six weeks, originally three times but later twice daily. The dose of reserpine was 10–15 mg. daily by mouth. Regular examinations for side-effects and toxicity were made and the patients' clinical state was rated at the end of each six-weekly period. The results indicated that in these conditions chlorpromazine was the drug of choice, not merely because the degree of improvement was greater but principally because the toxic or side-effects of reserpine in these doses were much more troublesome. The undesirable effects included marked restlessness, incontinence of urine and fæces, sialorrhœa, bulimia, œdema of the face, convulsions and, most frequently, a well-marked extra-pyramidal syndrome.

The early reports on reserpine emphasized the relatively trivial nature of adverse reactions associated with its use. With the small doses used in the treatment of hypertension the commonest symptoms—lethargy, nasal obstruction, aching legs, and diarrhœa—were not regarded as more than inconvenient. Only when sufficient time had elapsed for therapy to continue over several months was it recognized that a small proportion of hypertensive patients, between 5% and 10% in most reports and frequently with a history of previous psychiatric disorder, developed psychiatric symptoms which were usually of a depressive nature and often severe enough to call for E.C.T. (*Brit. med. J.*, 1955). Larger doses have been employed in neuropsychiatric practice, where the wide variation in dose-schedule indicates the empirical nature of the treatment. At one extreme 60 mg. daily have been administered to mental hospital patients (Kinross-Wright, 1955); elsewhere 2–5 mg. daily have been considered adequate for comparable populations (Kovitz *et al.*, 1955; Rinaldi *et al.*, 1956). Barsa and Kline (1956) have proposed an initial daily schedule of 5 mg. intramuscularly and 3 mg. by mouth. The advocates of every regime, however, recognize the idiosyncrasies and unpredictable responses of individual patients and modify their doses constantly. During treatment some patients have suffered from an exacerbation of peptic ulcer symptoms, including perforation; the hyperchlorhydria induced by the drug has been studied experimentally (Schneider and Clark, 1956).

Convulsions are now also recognized as a complication of treatment serious enough to contra-indicate E.C.T. during the period of drug administration (Foster and Gayle, 1955); experimentally, again, the drug has been shown to lower the seizure threshold in animals (Chen and Ensor, 1954). Other disquieting complications of reserpine treatment which have been reported include cardiac failure, orthostatic collapse, dyspnœa, hypothermia and thrombophlebitis, but none of these reactions occurs so frequently during treatment as the group of symptoms which, when fully developed, make up a neurological picture with all the features of post-encephalitic Parkinson's disease. While it has been shown that patients who were treated with doses of more than 30 mg. of reserpine daily all developed Parkinsonian symptoms (Kinross-Wright, 1955), quantity cannot be the sole determining factor since some patients react in this way to doses of no more than 5 mg. daily (Stead and Wing, 1955). Whether the neurological symptoms represent inconvenient side-effects of reserpine or provide evidence concerning its site of action remains undecided. The recent demonstration that these symptoms can be produced in primates by large doses of reserpine may provide an experimental approach to this question (Windle *et al.*, 1956; Cole and Glees, 1956). Since clinical experience meanwhile does not suggest that a favourable response to reserpine is dependent on the appearance of extra-pyramidal symptoms, continued administration of the drug beyond this point is inadvisable while doubt exists about the possibility of irreversible changes.

Finally, reference should be made to the numerous clinical studies on reserpine which have been reported or are in progress. The drug has been used to treat most of the major psychiatric syndromes and also conditions as dissimilar as rheumatism, Huntington's chorea and enuresis. The majority of published studies report on the therapeutic results obtained with in-patients. Those which are favourable emphasize that symptomatic improvement rather than cure should be expected but they are less precise about the indications for treatment. Mielke's report from the university clinic at Zurich may be cited as one of the most clinically explicit; on the basis of his experience with nearly four hundred patients he presents

the following list of symptoms as provisional indications for treatment: states of excitement, tension, feelings of unrest, stupor, negativism, mood changes and compulsive drives (Mielke, 1956). Other authors have employed non-clinical indices of improvement like seclusion rates or the number of ward disturbances. In view of the emphasis on environmental factors which is implicit in the choice of these criteria little has been done to evaluate the powerful influence of the hospital or ward milieu on the behaviour of the patients treated. The interaction between the effects of reserpine and those of a group situation on the organism has been demonstrated experimentally on mice by Christian (1956). At Netherne Hospital, where particular attention has been paid to the social aspects of mental hospital life and where reserpine has been administered to socially disturbed patients, the milieu in which treatment was given has proved to be a potent factor in determining the response of patients (*Lancet*, 1956; Wing, 1956). Observations of this type may help explain the discrepancies in the results obtained with reserpine by workers in different hospitals.

Three questions remain unanswered by the many studies which have been carried out: firstly, whether a particular, self-terminating illness runs a shorter and more satisfactory course than would have been the case if it had been untreated or treated otherwise; secondly, whether patients with previously intractable mental disease who respond favourably to reserpine do or do not relapse at a later date; and thirdly, whether those patients who are benefited by treatment differ in an identifiable manner from those who are not. Information of this type is notoriously difficult to obtain about psychiatric out-patients, and an assessment of their response to treatment has been rendered still more difficult by the tendency to combine the administration of reserpine with psychotherapeutic measures. Until these questions can be answered adequately reserpine will continue to stimulate interest among physiologists, pharmacologists and biochemists working on the central nervous system but clinicians will suspend judgment about its value as a therapeutic agent.

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United Services Section

President—Sir LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P.

[*March* 1, 1956]

DISCUSSION ON THE PROBLEM OF FEAR

Group Captain V. H. Tompkins:

The Meaning of Fear.—The first problem connected with the use of the word fear in military circles is the word itself. To the layman the word has an implication of cowardice although as Shaw pointed out, even though we die in our fear this does not prove that we are cowards. By definition fear is a painful emotion caused by danger or evil to which is attached certain characteristic bodily changes and behaviour. As well as frank fear of danger, fear as an emotion may develop in a situation where no obvious danger is apparent. McDougall stated the sequence in this fashion, "anxiety is the name by which we denote the state where the means we are taking towards the desired end begin to seem inadequate when we cast about for possible alternatives and begin to anticipate the pain of failure. Anxiety may be a normal reaction towards some special circumstances of which the individual is fully conscious. Not uncommonly the emotions of fear or anger become aroused when a difficulty becomes insurmountable". When these manifestations pass a certain threshold in relation to any circumstances a state of neurosis develops. The symptoms are exaggerations or distortions of the normal physiological accompaniments of fear. The whole neurosis is a perversion of the fear instinct.

Now fear demands a tone of feeling and will always be understood in this connexion by the layman. Although we, as medical men, may be happy to use the term fear in the absence of the feeling content and on the evidence of its physical accompaniments, we make it difficult for our concepts to be understood by the untrained. I can illustrate this difficulty by analogy. Epilepsy is, by definition of the Oxford dictionary, a nervous disease in which the patient falls to the ground unconscious, with spasms, and foams at the mouth. Once we extend the term to other types of attack which medically we know have the same basis we are in danger not only of being misunderstood, but of encountering active opposition to our views.

Much valuable work done in the last twenty years has failed to penetrate through to executive considerations because of this difficulty. Many Field Commanders consider it nonsense if told that most of the aircrew who broke down on flying did so because of fear since the manner in which they presented does not equate with their personal experience of this emotion, and breakdown continues in the absence of war conditions when overt fear is not the experience of the average man. While most aircrew will admit that from time to time they recognize the danger of flying few will admit to actual fear. Nevertheless in recent months I have been interested in discussions on stations that more and more pilots refer to occasions of fear while flying as normal and acceptable episodes. As a result they are showing an increasing interest in the highest degrees of fitness and skill. It is important, however,

that we should be sure we talk the same language, since it is only by whole-hearted acceptance of our views that we can get the help which we always require from administrators.

But since this is a medical presentation of the subject I must ask you, in spite of this caution, to accept that not only frank fear, but anxiety and the physical accompaniments which can be briefly summarized as tension, are proper subjects for our discussion.

No one can read the numerous autobiographies of war, nor can they live in combat with others, without realizing how universal is some degree of fear, or how equally present is its antidote—courage. It is when courage is exhausted that fear and its pathological exhibition prevail and total failure results. I do not propose to repeat at length observations which have been made already on the medical aspects of these failures. Suffice it to say that total psychiatric breakdown, whether in the individual or in a body of individuals, is equally devastating in its effects on all arms of the Service.

Royal Air Force Interest in Effects of Fear on Performance

From the Royal Air Force point of view it is in general fair to say that a special problem exists which is perhaps more urgent than in the other Services because of the highly complicated machinery involved and the small margin of error within which safety and efficient performance lies. Any small decrement of performance becomes important.

From the earliest days of aviation medicine the effects of fear and anxiety on diminished performance have been recognized. Our earliest leaders in the R.A.F. Medical Branch were the first to point this out. Birley, in his Goulstonian lectures, Head and Rippon, amongst others, described the effects of fear and especially emphasized its effect on efficiency in the air. The interesting literature on this subject has been critically reviewed by Symonds and Williams (1947) and repays study.

For the best part of the next vicennium there was little reason to refer to the lessons of the First World War. Progress in aviation was slow. I myself have served with squadrons equipped with First World War aircraft and those of the late 'thirties showed little increase in performance, whilst the requirements in aircrew were small and catered for with ease because good men to whom flying appealed had no easy outlet to other employment. It was not, therefore, until the immediate pre-war days that much further interest was shown in investigation of aircrew breakdown. At this time Burton and Dawson (1938) showed by a combination of psychiatric interview and air tests of suspended trainees that 85% of failures to learn to fly, whatever the supposed reason, could be related basically to anticipatory tension. Especially was this evidenced in so-called ham-handedness. These conclusions of Burton and Dawson were confirmed by a later investigation in America. Russell Davis (1948), to whose work I shall refer later, expresses this mechanism so well that I shall quote his words.

> "Anticipatory tension is often revealed in the demeanour of a subject at the beginning of a psychological test and in this case is related to the fear of failure to reach a satisfactory standard. *Usually* this tension is rapidly reduced if the subject has a degree of success; but if he is unsuccessful, danger becomes more imminent and tension is increased beyond the degree in which it is of value to him because it augments his efficiency. When a skill is being exercised, however, an increase of tension is a serious handicap and impairs efficiency. This, in turn, makes danger more imminent. A vicious circle is set up which is arrested either by complete breakdown or by a lowering of the standard to which the subject aspires, that is, abandonment of the previous goal.
>
> "Individuals may differ in the degree to which they regard a situation as threatening, in the degree to which tension is then aroused and, a given degree being aroused, in the degree to which it impairs efficiency. Generally speaking, however, the degree of tension and the impairment of a skill are determined by the apparent difficulty of being successful."

Some Royal Air Force Research into Effects of Fear in World War II

During the war years the R.A.F. Neuropsychiatrists under the leadership of Air Commodore H. L. Burton, Air Vice-Marshal Sir Charles Symonds and Air Commodore R. D. Gillespie collected observations on the Psychological Disorders of Flying Personnel which were later published by Sir Charles Symonds and Dr. Denis Williams who were responsible for most of the individual work. These observations were materially assisted by Squadron Leader D. D. Reid, now of the London School of Hygiene and Tropical Medicine. A major part of the book was an analysis of causes of psychiatric breakdown in aircrew. It was the finding that in 99% of the cases fear was the essential cause of breakdown and it was shown how eventual breakdown was a resultant of stress and robustness of personality.

Since, however, the average psychiatric breakdown rate among aircrew was only about 2% of the total aircrew strength such disorders were a minor cause of loss of personnel when

viewed against the reported casualties. In the course of the investigation, however, a method of assessment of predisposition to psychiatric breakdown on flying duties and, by implication, of liability to fear reaction was arrived at.

The method was based on a consideration of personal and family history and especially on reactions to life situations. It endeavoured to pick out evidence of leadership and stressed pursuit of games and occupations which may present an element of danger. Traits and events normally held to point to neuroticism were also considered. The procedure was empirical and personal but from assessor to assessor showed consistency, probably due to its broad spectrum and flexible assessment. For as Rook (1948) showed in his most valuable ten-year follow-up minor neurotic traits of physical type have by themselves no prognostic value for success in flying.

Using this method of assessment of predisposition, Reid (1942) studied the aircrew of two bomber squadrons and divided them into those he considered predisposed to breakdown and those with none or slight predisposition. The latter group acted as controls. He found that in the predisposed groups amounting to 18% of the total, failure to complete mission was 17% more frequent and their casualties 25% higher.

Most valuable observations into the effects of anticipatory tension were made by Russell Davis (1948) in his experiments with the Cambridge Cockpit which is a simple form of flight simulator. Russell Davis distinguished two types of abnormal reaction to his test—the overactivity reaction where the anticipatory tension produced gross inaccuracy and even emotional effects of excitement and anger, and the inertia reaction where the overactivity was succeeded by an emotional indifference and withdrawal. In the course of the Harrogate experiment the opportunity was taken to assess the findings against psychiatric assessment of predisposition. Since both psychiatric assessment and Davis' experiment were based on anxiety proneness, as would be expected the findings showed a similar trend. But the most interesting observations of Davis were in his follow-up. He found that 1 in 18·5 normals were suspended or killed against 1 in 7 of the abnormals. He found that there was one casualty to every 28 normal candidates while 1 in 6 of the inert became a similar casualty. Rook also found a double accident rate in his nervous candidates. It was possible to follow a small number of the tested sample farther. Of 53 pilots who reached operational squadrons only 3 of 41 of the normals became casualties against 5 out of 12 of the abnormals. Too small a number to be statistically valid but a striking suggestion of the importance of psychological stability in operational flying.

A further investigation of Reid's (1947) was his analysis of navigator performance under operational conditions. In this the operation logs of navigators were analysed for error and the errors equated with the stages of the sortie. The effect of anticipatory tension was seen in a steady deterioration in efficiency on the outward journey particularly over the enemy coast where there was almost always organized opposition and on approaching the target. This effect reached a maximum in the acute anxiety engendered by heavy enemy fighter opposition and persisted as long as the aircraft was over enemy territory. He also made the most important observation that discrepancies between ground and air training are probably due to a similar effect and that this may well be a pointer to diminished combat performance.

In a valuable discussion on pressure suits by Roxburgh and others (1956), attention is drawn to the similarity of the collapse in pressure breathing to vaso-vagal syncope—a known neurotic reaction—and the role in these collapses of hyperventilation, a physiological accompaniment of tension. Roxburgh states that fear or dislike of the situation can precipitate a collapse and especially records the adverse reaction of a candidate who had a history of claustrophobia. It seems likely, therefore, that an additional reason is emerging why anxiety proneness may be of great importance.

With the increasing complexity and expense of war machines the time will come when we must stress quality in aircrew far above quantity and must continually remind ourselves of a fact which peace-time tends to obscure, that the ability to drive an aeroplane is probably a minor factor in making an operational pilot.

Clinical Presentation of Fear

Fear as an instinctive response, as of a mother for the safety of her child, of the forces of nature and the private fear of death, is universal and may at times be overwhelming. But in my experience, expressed fear as a symptom is rare. It occurs in some toxic and severe affective disorders and the connexion of fear with heart disease in the pervigilium or as angor animi is classical. I do not propose to mention fear as a cause of panic states, or as a trigger

for epilepsy and other causes of unconsciousness, or as a factor in airsickness as these are covered by Dr. Williams.

The most common clinical disorder which has been related to fear in aircrew is a neurosis usually of anxiety type which corresponds in detail with those seen in everyday practice. However, from time to time fear as a symptom is met with in aircrew and I should like briefly to discuss two special types. Firstly, fear of flying as a calmly expressed fact, and, secondly, fear occurring as a circumscribed episode.

Fear of flying frankly expressed is seen in two classes of person, firstly and briefly, in persons of poor morale and personality who, by virtue of danger involving themselves or their acquaintances, develop a state akin to Russell Davis's inertia reaction and are incapable of placing themselves again in a danger situation. These people come almost entirely from the section who in their past life will be found to have avoided dangerous pursuits.

The second group of people who express frank fear is composed of mature aircrew who often without any special precipitating cause suddenly say they are afraid of flying. Sometimes they give as an excuse the view that they have lost confidence and it is not fair for them to be responsible for a crew, but usually they neither offer reason nor show any signs of persistent anxiety.

So far I have been able to form no firm conclusions about such cases, but I think it possible that a mechanism to which Bartlett (1943) drew attention may be the basis. He showed firstly that the prolonged exercise of skilled performance resulted in a reduced capacity for performance which can be measured under experimental conditions. Skill fatigue, like other fatigue, is cumulative in its effects so that it may appear suddenly. It is also liable to facilitate so that after inadequate rest fatigue will appear sooner than it did before.

The result of fatigue is usually insidious in its onset and more often presents as the basis for anxiety symptoms where morale has made a man push himself to the limit. I am satisfied, however, that from time to time the man of insight recognizes its effects and his impaired performance and thereby develops an active realization of his danger which he expresses. It is to be noted that once the severe effects of fatigue overtly develop the resistance to fatigue is permanently impaired on the exact analogy of a piece of elastic or metal which, on over stretching, fails to regain its former length. Welford *et al.* (1950) showed this point in experiments on civilian aircrew when they demonstrated that measurable impairment of performance occurred at tasks met for the first time when fatigued, but that little or no impairment occurred when the tasks had previously been met in the non-fatigued state. This impairment was not removed on subsequent retesting after rest. Although Reid (1948) pointed out that the effects of anxiety are predominant over fatigue as factors affecting both health and morale in aircrew, nevertheless the effects of fatigue should not be neglected on this account.

More commonly, fear is expressed as a feeling of being shut in or fear of crowds and this is the common presentation in aircrew.

A typical case is that of a first-class athlete and experienced pilot. A few days after he had witnessed the death of his father from a ruptured aorta he had an episode in the air when he found difficulty in concentrating, felt faint and shut in. The symptoms progressed both in the air and on the ground so that when first seen he was unable to attend any social gathering for fear he would faint. Slow progress under psychotherapy for a year has relieved his symptoms.

A second pilot developed symptoms of a transient feeling of being out of touch with reality and a feeling of unexplained fear so that he wanted to rush away and be alone. This immediately followed the death of his sister from cerebral hæmorrhage.

The basis seems to be a rigid overconscientious personality often with timidity traits and sometimes when faced with a death threat of medical type. Allied to this presentation is the apparent neurotic overlay which so often occurs in the person of high morale who regards fitness as a duty and whose personality seems to disintegrate under minor medical disability, especially in cases where prompt medical reassurance and explanation have not been given.

For instance a senior pilot of 40 years of age with a distinguished war record and a clean bill of health complained of neuralgic symptoms relative to cervical osteoarthritis. He was passed from hand to hand for confirmation of his diagnosis and by the time he was seen was in a state bordering on panic which needed prolonged support for its dispersal.

This group of cases is important because it comprises people almost all of whom have proved themselves to be able and energetic and of the best type of officer material and yet at the same time I have had no success in curing them by the recognized means of therapy. The condition is self-determining under supportive therapy, but is likely to recur under non-specific stress.

These cases strongly contrast with similar symptoms in persons of varying personalities where the precipitating cause has been physical. For instance, a pilot who during the course of the war was shot up in a four-engined bomber. On attempting to bale out his parachute jammed and he was left struggling, hanging to the side of the abandoned aircraft, before finally releasing himself and making a safe landing. After a short time as a P.O.W. he was repatriated and on return to flying duties had occasional episodes of mild nature when he would feel shut in the aircraft and a desire to escape. These became more frequent and intense so that he sought medical aid. A series of ether abreactions in which he relived his experience released his symptoms and when last seen he had some 900 hours uneventful flying.

Difficulties of Selection Procedures

So far I have mentioned the clinical presentation of fear and the effect of fear on efficiency. I have presented evidence that the anxiety-prone and those assessed as predisposed to breakdown on aircrew duties show higher casualty rates than the average, that they are less accurate and more prone to fail on missions and that they have a higher accident rate. I have produced evidence that beneath the overwhelming effect of anxiety there is a background decrement of flying efficiency caused by fatigue. Each facet seems to point to a definite personality type as being more liable than the average to these defects. What are the answers to this problem? Although a variety of tests have been evolved which correlate to a large degree in measuring emotional lability and control few have been validated as competent screening procedures and I can find little evidence of their application in selecting people with a view to grading the tasks they are likely to be most fitted for and the general approach to them seems to be as a mechanism for rejection for flying training. The most successful so far seem to be those such as the Cambridge Cockpit and the grading test (where candidates were classified in accordance with the time they took to fly solo), which, as nearly as possible, reproduce actual flying conditions in the test situation.

These methods of investigation which have yielded such valuable results are probably unworkable as selection procedures because they make a heavy demand on trained personnel for their application.

In the main, conclusions have been handicapped by lack of opportunity for full follow-up and, in part, by the setting of ability to learn to fly as the criterion for performance. There is no doubt of the excellence of aptitude tests for selecting ability to fly, but in operational flying it seems likely that temperament is more important than aptitude.

Equally is investigation into temperament handicapped because we are dealing with a labile situation so that even if we consider a personality as a circumscribed item it is difficult to lay down the degree of stress likely to be encountered or the fluctuation of other influences such as morale which are fundamental in producing personality reactions. Resistance to stress depends so much on the mood and pattern of thinking of the moment.

Useful as empirical assessment of personality and predisposition to breakdown has proved itself in the hands of Sir Charles Symonds and his colleagues as a research tool, it is not in my view in its present form a practical selection procedure. In the first place, few assessors of the required experience and aptitude can be found. There is no doubt also that conclusions arrived at can be biased both by knowledge of successful performance and by selective recall of possible predisposing factors after the onset of psychological disorders as well as appearance of latent neurotic tendencies under stress. The keen candidate will also often be far from frank so that the control series is not entirely reliable (Grinker *et al.*, 1946). Nevertheless I am sure that this work should be pursued on a research basis with the hope of finding a method free from such objections.

Prophylaxis Against Fear

Our endeavours to deal with the effects of fear must for the moment be prophylactic and supportive. As was shown by Stanbridge (1951) in relation to the Berlin Airlift, such methods are easily forgotten or overlooked. I should like to mention them in the briefest possible fashion. The prophylaxis against effects of fear can be divided into two approaches. The first is that which encourages the development of antidotes to fear and the second that which diminishes situations liable to cause fear.

First there is the attempt to encourage the development of fortifying factors in the men exposed to fear. This entails encouragement of the right kind of leadership by the development of group-spirit in the unit, particularly in respect to the maintenance of high confidence of the aircrews in their ground-crews, in their aircraft and in their leaders. It also involves attention to the mode of living of the aircrews, encouragement of physical fitness and of an

orderly method of living, as well as the limitation of fatigue. Special attention must be paid to comfort in the provision of living and recreational facilities and continuous instruction in the use of equipment must be given so as to instil confidence.

Secondly, every effort is made to limit the fear-provoking situations as far as is possible. It is, of course, impossible to limit the hazard of operational flying which results from enemy action, but navigational and technical aids to the aircrew are pushed to a high degree of perfection, with the object of reducing the hazards of flying in all weathers.

It is possible to reduce the anticipatory tension that comes before the operational flight in several ways. The crews are informed of details of the flight and target shortly before starting and after they have had a meal. The time of waiting in the aircraft and on the ground is reduced as far as possible and cancellation of sorties, which is sometimes unavoidable, is reduced to a minimum. A sortie cancelled at the last moment may result in almost as much tension as an actual trip.

The actual duration and intensity of the fearful period must also be controlled by the executive. A limit to the number of operational sorties expected of each man is laid down—a limit within the reach of the average and known to the crews. The operational limit is modified from time to time according to the nature and circumstances of the operational flying.

By comparing squadrons operating side by side but employed on differing duties on several stations, I was able to render a report at the end of 1940 which showed that the danger of flying as measured by the type of work and casualties incurred was a major factor in breakdowns and that where these were comparable a critical rate of flying could be arrived at above which breakdown occurred. Total flying hours played only a minor part and local conditions played no part.

Although there is a fixed upper limit to the operational duty expected of any one man, the Squadron Commander is encouraged to terminate any man's tour before that limit is reached, if he is satisfied that that man's reasonable and efficient contribution to the operational effort has been made. In this way the psychologically less robust are safeguarded and their efficiency is preserved for their second tour of duty.

The intensity of the hazard within the tour is reduced by spacing the number of operational sorties for any one crew and by resting a crew after a series of sorties with deep penetration into enemy territory, and to heavily-defended targets.

Finally, the effects of fear are reduced by frequent short leave periods, known beforehand and almost inviolate, which are spaced through the tour; by active programmes of entertainment and recreation and by creating a communal life.

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Dr. Denis Williams: *The Effects of Fear in Flying.*

Group Captain Tompkins has dealt as a serving officer with some of the ways in which the Royal Air Force tries to reduce the damaging effect of fear when it arises—for arise it certainly will—in flying, whatever steps are taken to improve methods of personality selection or to reduce the hazards of flying. I, too, am concerned with the effects of fear as it is seen in the Royal Air Force since it is there that I have had experience of it. As a civilian I will deal more with the inner and personal, and less with the administrative, aspect of the problem of fear.

Fear as a protective function.—The emotion, fear, is by its nature anticipatory—we are afraid that something is going to happen—even when we say we are afraid that something has happened, we are really expressing fear of the consequences. We are always afraid of the future, which is a good thing because it gives us and others the chance to take action, and in this sense fear is protective. Indeed when we continue to approach an increasingly dangerous situation fear becomes more and more intense. We have all experienced that phenomenon in dreams, for if we had been able to run faster than the lion we would not have needed to wake in increasing terror just before he caught us. Fear for an impending dangerous event is protective, and the Orbeli phenomenon, observed when prodigious feats are performed in flight or in combat, is due to the enhanced efficiency of muscular contraction in the presence of circulating adrenaline.

Darwin (1904) emphasizes the protective value of fear, saying that it motivates the animal to flight, or if that proves to be impossible, to defence. This point is recognized in practice, and Symonds (1943) quotes an experienced Squadron Commander who told him "that he liked a man to have enough imagination to fear the worst and hope for the best. Thus he could set forth on his operational sortie prepared for every hazard, and would be more likely both to succeed and to survive than the more phlegmatic types."

Fear as disruptive influence.—Though some degree of fear is advantageous, induces reasonable caution, increases perception and enhances physical reaction, excess may be disadvantageous, or even disastrous. Mosso wrote in 1896 "The phenomena of fear, which may be useful in lesser degrees, become morbid and fatal to the organism as soon as they exceed a certain limit: for this reason fear must be looked upon as a disease." The disintegrative effects of emotion have been much debated in recent years and Young (1949) considered an emotion to be an acute upset which led to disintegration of efficiency in some degree. Leeper (1948) on the other hand has argued—and there is wide agreement with him—that emotions, including fear, are adaptive and adjustive in their mechanism. They help the organism in the direction to which he is motivated. Group Captain Tompkins made the point, which I would like to re-emphasize, that there is a difference between overt fear, recognized by introspection in all of us, and the disastrous effects of a continued fear state that brings the man to the Station's Medical Officer and the psychiatrist. Not only has the emotion itself been more intense, but intervening secondary mechanisms, unrecognized by the layman, have been operative. *In this discussion, we as physicians are therefore concerned with an intensity of the emotion which we can with Mosso consider to be a disease.* The view has accepted precedents in other fields of medicine, for many abnormal states are simply intensifications of the normal; a little pain is a timely protection, too much a disaster.

Fear and anxiety.—It might be well to consider here the differences which stem from variations in the degree and the duration of fear. Freud (1936) made a distinction between anxiety and fear, and discussed the significance of free floating or unattached anxiety. There are many others who consider that anxiety is simply "fear spread thin" and that view is held by academic psychologists interested in the subject. The intensity of fear may range from apprehension through worry and anxiety to fear and terror. It is apparent, though, that the nature of the emotion felt also depends on other factors than the intensity alone—there is the underlying mood or feeling tone, its duration, and the imminence of the fear-provoking event. This has practical value in our discussion, for the damaging effects of prolonged anxiety may be as disastrous as those of immediate terror, though their nature is different.

The visceral component of fear.—It is in the emotion fear more than in any other that the intimate association of bodily change and subjective state is apparent. James and Lange independently in 1884 and 1885 argued that the experience of the emotion resulted from bodily changes that had arisen—a view modified later by Cannon (1927) who pointed out that we feel afraid, before the more slowly-operative visceral changes can have become apparent to us. With Head he proposed the thalamic theory of emotions which allows us

latitude and flexibility, in that the suggestion is that the visceral components of the fear-state are mediated through thalamic interconnexions—the motor and sensory components of the fear state are closely related to each other, both inherent in the event, yet not wholly interdependent. What is important to us in the United Services Section is that the bodily components of fear are part of the emotional experience and cannot be suppressed, however brave we may be. *Courage consists in pressing forward despite personal proof of this fact.*

Sherrington wrote (1948) "To the ordinary day's consciousness in the healthy individual the life of the viscera contributes little at all, except under emotion . . . yet heightened beating of the heart, blanching or flushing of the blood vessels, the pallor of fear, the blush of shame, the Rabelaisian effect of fright upon the bowel, the secretion of the lachrymal gland in grief, all these are prominent characters in the pantomime of natural emotion."

In thinking of the way fear affects the combatant we must, as we have already been told, consider those things that modify the development of fear, and the response to it (what Moran (1945) in his little book on Courage called "The Birth of Fear"). The kind of stress is presumably important, and as we are here using experience with flying personnel it is only necessary to refer your attention to statistics in the Air Ministry publication 3139 "Psychological Disorders in Flying Personnel" which show a close direct relationship between the danger of the task, measured by survival time, and the occurrence of breakdown. But this study was a statistical one and statistics involve large figures. The difference in the different stations, squadrons, crews, and men making up those large, consistent figures was, however, found to be marked. Clearly, therefore, environment—social, physical, and spiritual—is supremely important in causing deviation above and below the average, but I cannot dwell upon that. Then the factors affecting the response to fear consist in the kind of man who experiences it—both psychological and physical, and upon his setting to which I have already referred. The value of leadership, example, and forethought in raising morale has occupied many writers, but it is our privilege here this evening to need no such script for we have seen it for ourselves.

The response to fear.—In considering what may happen when fear has escaped and taken charge, either because the stress was too great, the individual too vulnerable, or the group inadequate, let us accept the ordinary physiological concomitants of the fear-state to which I have referred earlier because we have all experienced them and have read about them. The response may be in the body (somatic) or in the individual or group behaviour.

Behavioural.—First *sustained fear which is overcome* produces a reaction in behaviour well seen in operational stations in the war. The return to base, the release of tension, the heightening of feeling caused by repeated experiences of a similar kind, charged the whole atmosphere of the Officers' and Sergeants' Mess. It was so natural and so essential that it continued as long as the stress, so that although the Royal Air Force recruited from exactly the same population as other Forces it gave a recognized "Air Force Type," emotional, uninhibited, and hearty. This was known before handlebar moustaches, for Herbert Spencer in 1863 described the use of laughter in releasing tension and said "Strong feeling, mental or physical, is the general cause of laughter". Mirth is caused by the agreeable feeling that follows stress (McKellar, 1952). Darwin, too, in 1904 referred to the release of emotional tension achieved by laughing. In the Royal Air Force not just men, but squadrons and stations behaved in this way.

The second kind of behavioural response I would like to mention is that of *inefficiency*—the failure to take appropriate or wholly adequate action in a state of fear, the navigator who could not calculate, the rear-gunner who fired tracers into the night sky at enemies of his own making, the pilot who failed to press home his attack, dropping his bombs as the news bulletin had it of the Germans "at random".

The third is *flight*—either actual physical flight, or dissociation in which there is immobility and subsequent amnesia, which may be penetrated by abreaction. There is also closely related to this the extraordinary state of trembling rigidity under great stress, which seems to be the ultimate disintegration that can occur with fear. Moran describes such a condition which he saw in a sergeant of excellent antecedents under great stress. We met it in air-gunners who were found rigid, mute, and apparently stuporose in their turrets, having failed to reply on the intercom.

Somatic.—We need not here deal with the minor exaggerations of the usual physiological components of the acute fear-state—explosive defæcation, micturition or vomiting, disturbances of heart-rate, and other symptoms which added to the horrors of day- and night-bombing. The most important is emotional overbreathing, for its effects are so far-reaching.

In passing, we should recognize the distinctions that can be made between constitutional air sickness, and the visceral accompaniment of fear.

In a survey of causes of periods of unconsciousness, confusion and amnesia while flying in the last war I studied 100 such cases, and it is important for our present discussion that 76 of them occurred during operational flying, though the total so employed at any one time was a minor proportion of all aircrew (Williams, 1947).

More than half of these episodes were known to be due to fear, and in some of these fear actually caused an epileptic fit (Table I).

TABLE I

Cause of Unconsciousness, Confusion or Amnesia while Flying

	No. of cases	
Psychogenic:		
Fear or anxiety state	43	
Panic state	2	
Hysteria	10	
Fatigue state	2	
	—	57
Epileptic:		
Epilepsy (including symptomatic)	23	
Probable epilepsy	9	
	—	32
Other physical causes not relevant to this discussion ..		11

None of the 32 who had had a convulsion had ever had an attack before, and it is important for our present discussion that three-quarters of these happened on bombing operations, where danger was so great. It is very important that many occurred near the target area. One of the more common mechanisms was that of fear leading to over-ventilation in a person predisposed to convulse. Such a case was as follows:

Case 66: *Fear causing an epileptic fit.*—An airgunner, aged 20, was on his tenth trip to Kiel an hour from base at 13,000 feet on oxygen, sitting beside his pilot. He felt tense, nervous and very afraid. His tongue was dry, he was sweating, had palpitation and then had a feeling of suffocation and could not get his breath. He then developed a pain in the chest "over the heart" of a gripping, cramp-like quality. The sweating increased, he began trembling violently and his hands would not stay still. The captain saw he was blue and the patient told him he did not feel so well. He then lost consciousness and recovered on the rest couch twenty-five minutes later. During this time he had "a twitching type of convulsion mostly in the legs. He frothed at the mouth and dribbled saliva". When the airgunner regained consciousness he felt tired and had a headache, and the aircraft was returning to base. Ten minutes after landing the Medical Officer could find no abnormal physical signs.

Overbreathing of this kind may continue and lead to confusion without an actual convulsion as in the following case.

Case 39 was an example of unconsciousness caused by fear in a timid airgunner. A timid, unstable, anxious man, both of whose parents were nervous and equally unstable, volunteered for aircrew. Great fear was experienced on the first two operational trips, and an acute anxiety state developed. Before the third trip he reported sick but no disorder was found and he was sent on it; an acute fear developed within an hour of taking off. He was seen to be sweating and overbreathing and had amnesia for the next forty-five minutes. There is not enough evidence available to determine his state of consciousness or the intermediate mechanisms initiated by fear which produced it.

Fear may also cause *tetany*, as in a pilot aged 20 who had five attacks while night flying, in which his arms felt stiff, then his hands became stuck to the controls as if he were held from the elbow down. He would then have difficulty in moving, he could not read his instruments, and in the last attack his Wellington stalled, the bomb aimer had to wrench his hands off the controls, and found that they were stiff. The pilot was unaware of any change of respiration, but when examined later he was found to have an anxiety state, and four minutes' hyperventilation produced Chvostek's sign.

The men in this series of a hundred examples of loss of consciousness, confusion and amnesia, with known fear states, with those who had had fits for the first time while in the air, constitute over 80% of the total and more than three-quarters of these were flying on operations when the attack occurred. We were so impressed with the occurrence of the period of confusion or the convulsion near the target that a respirometer was fitted to the oxygen apparatus of a normal member of a bomber crew on an operational trip. It was found that overbreathing occurred on crossing the Dutch coast, increased and became

intense near Berlin, and ceased on the journey home. The subject of that study made no complaints and was just a normal member of a bomber crew doing his job, but we had certainly observed one of the visceral effects of his fear, a visceral effect which in another man might have had disastrous results.

One of the conclusions of that report was that "By far the most common primary cause of impairment of consciousness in the air is fear".

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Sir Charles Symonds: I cannot quite agree with the view that a man who persists with a task despite fear will break down or lower his goal. He may, by the exercise of courage, become conditioned and achieve a state of fearlessness. Nor can I subscribe to the view that fear is necessarily anticipatory. There can be retrospective fear, as when a man has just escaped a sudden danger whose full implications could not be grasped at the moment of its happening. Under such circumstances the imaginative man may suffer fear after the event. Moreover in some persons—and I think this is a constitutional liability—the visceral effects of fear, for example, tachycardia, may persist long after the affective disturbance has faded. There is perseveration of the bodily reaction.

The administrative problem of disposal of men for whom fear has become a disease is difficult because the criteria of morbidity are social as well as medical. The social criterion is determined by the amount of courage and fortitude a man must be expected to show in persisting with his task despite fear. The problem in a fighting service is quite different from that in civilian life. There may, therefore, be discrepancies between the medical and the executive points of view. A medical board may decide that a man is permanently unfit for flying duties owing to an anxiety state, when the executive opinion is that others with equally severe symptoms are able to carry on with their duties. During the last war this problem was dealt with in the Royal Air Force by close collaboration between medical and commanding officers at every stage from the Station upwards, and at the Air Ministry level the reports in any doubtful case were examined by a senior executive officer and one of the consultants in neurology, the final disposal of the man, whether, for example, he should retain or lose his flying badge, being a matter for executive decision, guided by the reports of medical officers and specialists, and the reports of commanding officers. This plan worked very well.

Section of Experimental Medicine and Therapeutics

President—E. E. Pochin, M.D., F.R.C.P.

[*February* 14, 1956]

DISCUSSION ON CLINICAL AND EXPERIMENTAL STUDIES WITH RADIOACTIVE IRON

Dr. L. F. Lamerton, Dr. E. H. Belcher and Miss E. B. Harriss (Physics Department, Institute of Cancer Research, Royal Cancer Hospital):

Radioactive Iron Studies in Normal and Irradiated Rats

Introduction.—The experimental work to be described is concerned with the metabolism of administered radioactive iron in the normal rat, and in the rat whose bone-marrow has been affected by irradiation or by the administration of various drugs. A number of these studies have parallels in clinical applications and the comparison is of interest. In certain types of investigation the animal work can, of course, go much farther than the clinical work, for instance in tissue turnover studies. Also, it is possible to give large doses of radioactive iron, which would be quite prohibitive clinically on account of the possible long-term hazards, and therefore to employ techniques such as high resolution autoradiography of red cells and red cell precursors.

Iron uptake and turnover studies in the normal rat.—The technique for determining iron distribution and turnover curves in the various tissues of experimental animals is not a difficult one. The iron can be administered and after a given interval the animal exsanguinated, dissected and whole tissues and organs counted directly in a well-type scintillation counter.

Parenteral administration of radioactive iron labels the iron in the metabolic pool, part of which is utilized by the bone-marrow for hæmoglobin synthesis. Thus the iron turnover curve in the erythropoietic tissues will show a maximum, at a time determined by the rate of uptake of iron and the rate of release of iron incorporated in newly formed red cells.

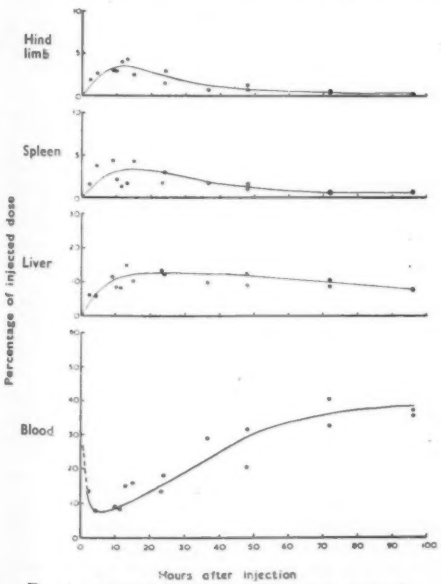

FIG. 1.—Iron turnover in normal rats injected subcutaneously with Fe^{59}.

Fig. 1 shows the iron turnover curves for certain tissues of the young growing rat given radioactive iron subcutaneously. Taking the hind-limbs as representative of the bone-marrow throughout the body it can be seen that maximum uptake is achieved after about ten hours (the interval is somewhat less after intravenous injection) and that a large part of the iron has been cleared by forty-eight hours. In the rat the spleen also has a degree of erythropoietic function and it can be seen that the shape of the spleen turnover curve is similar to that of the bone-marrow, but with the maximum occurring rather later. For a quantitative treatment of these results it is necessary to know the fraction of the total active bone-marrow contained in the hind-limbs. This can be determined by dissecting out and assaying the activity of the various parts of the bony skeleton of a rat given radioactive iron a few hours previously. The technique is relatively simple and can be used for determining the skeletal

distribution of bone-marrow in any small experimental animal. For rats we find the values to be very consistent, and mean values are shown in Table I.

TABLE I.—DISTRIBUTION OF Fe^{59} THROUGHOUT THE BONY SKELETON

	%		%
Spine	30·4	Sternum and ribs	5·3
Femur 2	16·6	Radius, ulna and fore-foot 2 ..	3·5
Tibia, fibula and hind-foot 2 ..	10·8	Scapula and clavicle 2	3·4
Pelvis	10·6	Tail	1·2
Humerus 2	7·3	Skull	10·9
		Total	100·0

It will be seen that the hind-limbs contain 27% of the total active bone-marrow. Thus, referring back to Fig. 1, about 50% of the radioactive iron injected is taken up by the bone-marrow and spleen and about 50% by the remaining tissues.

The turnover curve determined for the liver shows that about 10% of the injected dose of iron is taken up by this organ, and is released only very slowly. It appears that the release is also slow from the other non-erythropoietic tissues since the final activity appearing in the blood is approximately equal to the total amount of iron taken up after injection by bone-marrow and spleen.

The rate of appearance of activity in the red cells of the peripheral blood is shown in Fig. 2. There is an initial rise in the red cell activity which occurs while the plasma activity

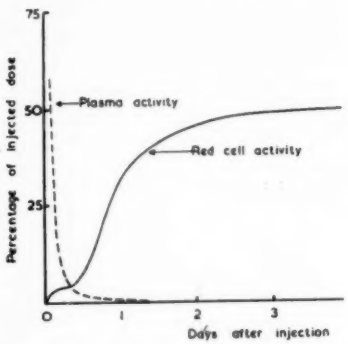

FIG. 2.—Plasma clearance and red cell uptake of intravenously injected Fe^{59} in normal "August" rats.

of the blood is still at a high level, and we have shown by *in vitro* measurements that this corresponds to a direct uptake of iron into the circulating reticulocytes. The rise in red cell activity due to the emergence of newly-formed red cells from the erythropoietic tissues becomes appreciable six to eight hours after injection. The blood activity curve flattens out about two days after injection, showing that appreciable amounts of iron are not taken up by red cell percursors earlier than two days before their emergence into the peripheral blood, a conclusion confirmed by the turnover data. From the shape of the blood uptake curve it appears that the maximum rate of iron uptake in the marrow occurs in red cell precursors within one day of emergence.

To determine the iron uptake in individual cells one can use high resolution autoradiography. The low energy of the β-radiation makes Fe^{59} a particularly suitable isotope for high resolution autoradiography (Lamerton and Harriss, 1954; Lamerton *et al.*, 1954). Our own autoradiographic studies of bone-marrow are by no means complete, but present results show that iron is taken up by all forms of normoblasts (except perhaps the oxyphilic normoblasts) and by the reticulocytes. All forms are approximately equally active one hour after intravenous injection indicating that their rates of iron incorporation are approximately the same. The autoradiographic studies should also allow one to determine the rates at which the red cell precursors pass through their different stages, but work on this aspect of the problem is still in progress.

Comparisons of iron metabolism in rat and man.—There are interesting differences between the pattern of iron metabolism in rat and man. In the first place iron turnover in the bone-marrow is much more rapid in the rat. This affects the shape of the blood uptake curve which in man takes seven to ten days to reach its maximum value. Also in man the first part of the curve is concave, indicating that the iron uptake of the precursors is at its maximum

some days before their emergence into the peripheral blood. Nevertheless, we have been able to demonstrate a direct uptake of iron into the reticulocytes of the peripheral blood of man, though the rate of uptake is several times less than for the rat. Autoradiographic studies of iron uptake in human red cell precursors have been carried out by Drs. Lajtha and Suit of Oxford (1955), using bone-marrow cultures, since the doses of radioactive iron needed are too large for *in vivo* work. Their results indicate that there is a maximum iron uptake in the early dividing forms (pronormoblasts and basophilic normoblasts) which differs from our findings with rats. It is not yet clear whether this is a result of difference in experimental techniques, or whether it represents a true species difference.

An important difference between rat and man lies in the erythropoietic function of the spleen in the normal rat. As we shall see later the rat spleen has the capacity for greatly increasing its erythropoietic activity under certain conditions, and this is an important factor in determining the response of the animal to agents such as ionizing radiation.

Excretion of iron and red cell survival.—Some interesting results may be obtained from the application of Fe^{59} techniques to the study of red cell destruction (Belcher and Harriss, 1956). Parenterally administered Fe^{59} labels a group of red cell precursors of nearly the same age, in contrast to Cr^{51} or P^{32} labelling techniques where cells of all ages are labelled. By studying the fate of this labelled cell group one may distinguish between random destruction mechanisms, affecting cells of all ages, and the eventual breakdown due to senescence of cells surviving random destruction hazards.

A small fraction of the radioactive iron returned to the metabolic pool as a result of the breakdown of labelled cells is excreted, the rest being re-utilized. If the labelled cells are to be studied by the assay of serial blood samples, this re-utilization must be blocked by large doses of inactive iron. However, other methods of study are possible where re-utilization does not interfere and need not therefore be blocked. For example, fæcal excretion can be used as an index of red cell breakdown, and in Fig. 3 examples are shown of the pattern of

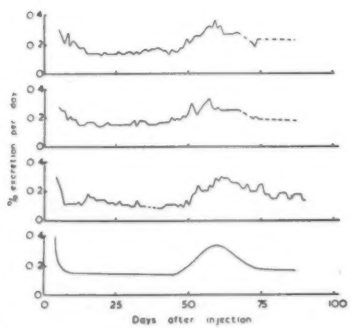

FIG. 3.—Fæcal excretion of Fe^{59} by normal rats. The lowest curve shows the theoretical pattern of excretion assuming a random destruction of 1·4% per day, 20% re-utilization and a potential life span of 55 days.

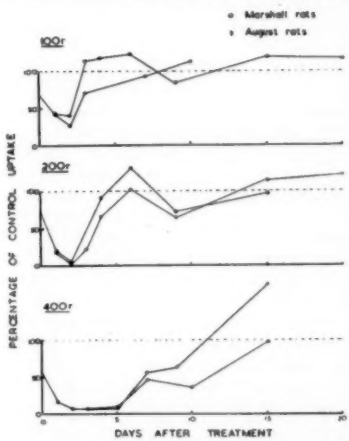

FIG. 4.—Uptake of Fe^{59} in circulating blood of "August" and "Marshall" rats twenty-four hours after subcutaneous injection, animals being injected at various times after 100 r, 200 r and 400 r whole-body X-irradiation.

excretion obtained in the rat after the injection of a single dose of 10 μc Fe^{59}. Immediately after injection, excretion is fairly high (about 1% of the original dose per day) as iron is cleared from the plasma and storage sites. However it soon falls to a level of about 0·1% per day representing a constant random destruction process, which is maintained up to about 50 days. Hereafter, fæcal excretion increases by a factor of 2–3 to a broad maximum representing the breakdown as a result of senescence of those cells surviving random destruction. These data indicate a random destruction rate in the normal rat of 1·4% per day and a potential life span of 55 days. After splenectomy, the potential life span is increased to about 70 days. Injection of phenylhydrazine causes an immediate increase in fæcal excretion due to enhanced random destruction. It may well be that this method could be used to study red cell survival in man.

Similar results are obtained by autoradiographic studies in which the percentage of active cells remaining in the blood at different times after the injection of radioactive iron is determined. The percentage of labelled cells in the normal rat shows a sharp fall at about 55 days; again after splenectomy the potential life span is increased to about 70 days.

Effects of irradiation on iron metabolism.—As demonstrated first by Hennessy and Huff (1950), radioactive iron uptake in the blood may be used as a criterion of the bone-marrow impairment produced by radiation. These workers showed that, in rats, the uptake of radioactive iron in the red cells of the peripheral blood is depressed by whole-body radiation given prior to the injection of the iron. We have not been able to confirm the claim made by these authors to detect the effect of a dose of as small as 5 r, given forty-eight hours before the injection, but have shown that, using groups of 5 rats, a dose of 25 to 30 r given twenty-four or forty-eight hours before injection causes a significant reduction in the twenty-four hour blood uptake, that is, the percentage of the injected dose appearing in the blood twenty-four hours after administration (Belcher *et al.*, 1954; Baxter *et al.*, 1955).

This is a very attractive application of a radioactive iron tracer technique, since it provides a sensitive criterion of bone-marrow impairment which can be used not only for studying the effects of radiation but also of various drugs which affect the bone-marrow. Its usefulness, both in experimental work and in possible clinical applications, depends, however, on a knowledge of the mechanisms involved, which are by no means fully understood. In an attempt to learn something of the mechanisms we have followed the iron uptake in the blood with various intervals between irradiation and injection of iron. Fig. 4 shows the twenty-four-hour uptakes at various times after irradiation with 100 r, 200 r and 400 r, whole-body exposure. Data are given for two strains of rats and there is seen to be very little strain difference. For all three dosages the curve falls to its lowest point, corresponding to the minimum output of new red cells, at about two days after irradiation. The depth of the minimum and the time for recovery depend on the dose given. With both 200 r and 400 r recovery is interrupted at six or seven days after irradiation. This is not an isolated observation, and we have found this pattern of bone-marrow recovery after irradiation in a number of experiments.

It is of interest to consider the final uptake in the peripheral blood. When iron is injected two days after irradiation at 100 r, 200 r and 400 r the fifteen-day uptake observed is below the control value. However, when iron is injected at the same time as the irradiation is given, the percentage of the injected iron appearing in the blood fifteen days after 100 r and 200 r is approximately the same as that of the controls although after 400 r it is still below the control value. This finding suggests that doses of up to 200 r do not seriously damage the red cell precursors which are capable of iron incorporation. These cells are, however, held up in the marrow, and their emergence into the peripheral blood is delayed. The reason for this delay is not clear. It might be a direct radiation effect on the later precursors, but for various reasons this is unlikely. Alternatively, it might be the result of environmental changes resulting from damage to the earlier dividing forms or of some humoral factor produced from irradiated tissue. After a dose of 200 r the minimum in the twenty-four-hour uptake curve occurs at two days after irradiation, suggesting that at this time there is a deficiency of cells in the iron-incorporating stage. It may be that many of the later forms which were initially delayed by the radiation have by two days emerged into the blood leaving a deficiency which is later filled up by a compensatory proliferation.

There are other possible explanations of the minimum at two days, such as the inability of the later forms to take up normal amounts of radioactive iron, because of their delay in emergence. The mechanism is still very conjectural and it may be that further histological and autoradiographic studies will make the process clearer.

Until the various factors are sorted out it is not possible to predict what will occur with other species. However, if the minimum uptake is due to a deficiency in the number of iron-incorporating cells, it is likely that in man it will occur at a longer interval after irradiation than in the rat owing to the slower maturation of the red cell precursors. It is not possible to say whether the radioactive iron technique will be as sensitive a criterion of radiation effects in man as in the rat. The small amount of clinical work that has been done on whole-body irradiated subjects (by Dr. Suit at Oxford and by Dr. Sinclair at Houston, Texas) suggests that it is not as sensitive.

Turnover studies in irradiated animals.—In the rat the spleen appears to play an important role in determining the pattern of recovery of erythropoietic function after radiation. Tissue turnover studies in rats made anæmic by a whole-body dose of 400 r show that the recovery of erythropoietic function starts in the spleen, and that bone-marrow erythropoiesis does not approach normal values until later. By contrast, we find that in rats made anæmic by bleeding, both spleen and bone-marrow contribute to the increased erythropoietic function in recovery (Baxter *et al.*, 1955).

The role of the spleen is also important in recovery following partial body irradiation, but the pattern of recovery differs considerably from that after whole-body irradiation. We have found that shielding part of the active bone-marrow of the rat, for instance a hind-limb, during radiation exposure reduces very greatly the severity of the post-irradiation anæmia. This is due, in part, to the maintenance of platelet count above the critical hæmorrhagic level, resulting from megakaryocyte activity in the shielded marrow, but iron turnover studies have shown up some interesting features in the recovery of erythropoietic function of the leg-shielded animal. We have carried out a systematic determination of the iron turnover curves for various tissues at different times after doses of 200 r and 450 r for groups of leg-shielded and of unshielded rats. During the first few days after irradiation the shielded limb has a very high iron turnover. This returns to normal within a few days, but iron turnover in the spleen of the leg-shielded animal increases in erythropoietic function earlier than in the whole-body irradiated animal. Full details of these studies will be published elsewhere, but two of the series of turnover curves, at two and at twenty days after

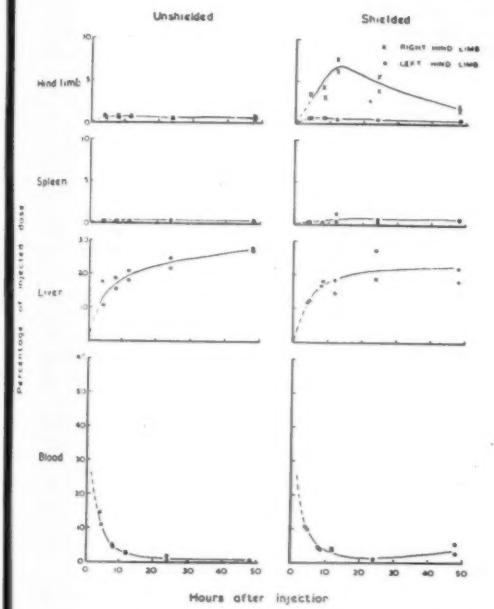

FIG. 5.—Iron turnover in whole-body irradiated rats and in rats irradiated with right hind-limb shielded, animals being injected subcutaneously with Fe^{59} two days after 450 r.

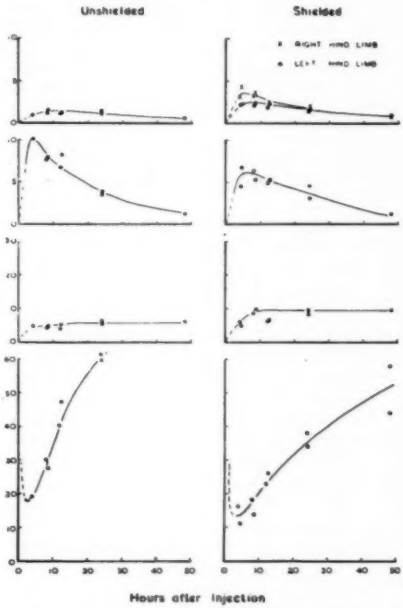

FIG. 6.—Iron turnover in whole-body irradiated rats and in rats irradiated with right hind-limb shielded, animals being injected subcutaneously with Fe^{59} twenty days after 450 r.

450 r, are shown in Figs. 5 and 6. The curves for two days (Fig. 5) show a very low iron uptake in the unshielded limbs and in spleens, and a high turnover in the shielded limb. The liver uptake is much higher in the control animals and very little radioactive iron is released into the blood. At eight days the unshielded hind-limbs had increased their turnover, and the spleen of the leg-shielded rat was more active than the spleen of the unshielded rat. At twelve days one could still observe the increased splenic iron turnover in the leg-shielded animals, while marrow uptakes were less than at eight days and considerably lower than normal. By twenty days (Fig. 6) the spleen of the unshielded rat has become very erythropoietic although the marrow has not yet recovered.

At the moment one can only guess at possible explanations of some of these findings, particularly with regard to the pattern of splenic erythropoiesis. It is possible that one may be observing the action of regenerative factors produced from the shielded limb, but there is as yet no direct evidence of this.

Summary.—Techniques employing radioactive iron have been used to investigate various aspects of erythropoiesis and red cell survival in the normal and irradiated rat. A special

study has been made of the pattern of iron turnover in the various tissues and the effect of whole and partial body irradiation.

Acknowledgments.—It is a pleasure to record our appreciation of the invaluable assistance given by Miss K. Adams and Miss M. Winsborough, and our thanks to Dr. L. G. Lajtha and Dr. H. D. Suit of the Department of Radiotherapy, Oxford, for many stimulating discussions. We are very grateful to Professor W. V. Mayneord, Director of the Physics Department, for his constant encouragement.

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Dr. Mary D. Smith (Radcliffe Infirmary, Oxford):

Clinical and Experimental Studies with Radioactive Iron with Special Reference to Iron Absorption after Partial Gastrectomy

Alimentary iron absorption has been studied before and after partial gastrectomy. No consistent diminution in absorption occurred after operation but isolated cases showed considerable reduction in iron assimilation.

Material.—Iron absorption tests were carried out on 28 patients with peptic ulcer from the Surgical Waiting List. Patients with anæmia or a history of frank blood loss before operation were not included. 21 patients were available for further study at six weeks and six months after operation. A further 27 patients were investigated at one to five years after a Polya-type of operation. 8 of these were found to have hypochromic anæmia and were treated with intravenous iron; in 6 absorption levels were re-estimated.

Method.—The test dose of 5 mg. elemental iron in the form of ferrous sulphate, labelled with 5 μc Fe^{59}, was given with 50 mg. ascorbic acid as a drink in the morning on a fasting stomach and fasting continued for another two and a half hours. The unabsorbed iron was estimated by counting the radioactivity appearing in the fæces (Badenoch and Callender, 1954). The iron not recovered was assumed to have been absorbed. The absorption was checked by estimating the amount of iron subsequently incorporated in the red blood cells. There was a consistent correlation between the fæcal and the blood results, although up to 15% of the administered dose was sometimes not accounted for.

Results.—In 10 normal subjects absorption ranged from 8% to 39% of the test dose with a mean of 26%. Repetition of the test under the same conditions showed variations of up to 23% in individual subjects. Iron absorption before operation in peptic ulcer patients ranged from 7% to 69% with a mean of 29%. After operation differences from pre-operative levels were often greater than the variation inherent in the test, changes of up to 43% being observed. The trend was towards diminished absorption but in individual cases this was not always maintained over both post-operative tests, and in a few instances there was a considerable increase in assimilation. In 3 cases, however, there was a reduction of over 30% in both post-operative tests, absorption falling to less than 10% of the dose given (Fig. 1). The wide range of absorption and the alterations after operation could be related neither to plasma iron concentration, to any possible depressive effect of blood transfusion at operation, nor to the type of ulcer present.

Of the 6 patients who had a Polya partial gastrectomy 5 showed a reduction in iron absorption. In the 19 other patients, however, who had had a Polya operation one to five years previously, and who were not anæmic, the mean absorption was 35%, which was slightly greater than for patients with peptic ulcer before operation. In the further 8 who were found to have iron-deficiency anæmia the mean absorption was 50%, although one patient whose hæmoglobin was 10 grams/100 ml. absorbed only 15% of the dose. This increase in absorption was in keeping with the mean of 67% for a group of 18 patients having hypochromic anæmia due to chronic blood loss but in whom the mean hæmoglobin level was slightly lower. After treatment of the anæmia with intravenous iron the absorption levels of the Polya patients fell to the lower limit of normal.

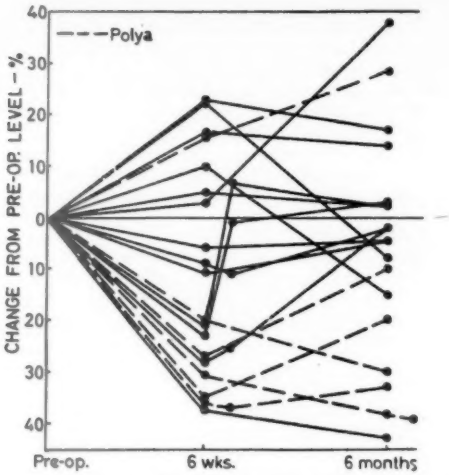

FIG. 1.—Changes in the level of iron absorption in 19 cases seen both at six weeks and six months after partial gastrectomy. Pre-operative absorption is represented as zero for each case.

Discussion.—It is generally believed that the stomach and duodenum are important sites of iron absorption and that excision or short-circuiting of these regions by partial gastrectomy may predispose to iron-deficiency anæmia. The results presented show that although there may be a trend towards diminished absorption of soluble inorganic iron after partial gastrectomy, there is no consistent decrease in iron assimilation, and only isolated cases show significant impairment of iron uptake. Patients with partial gastrectomy who have developed iron-deficiency anæmia do not show a malabsorption pattern but are capable of augmenting iron assimilation in almost comparable degree to patients known to be anæmic from chronic blood loss but having an intact alimentary tract. The evidence suggests that malabsorption of iron alone is unlikely to be the cause of iron deficiency after partial gastrectomy and that good iron absorption can take place beyond the duodenum. These studies have, however, presented ideal conditions for iron assimilation and it is possible that food iron is handled in a different manner.

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Dr. M. S. R. Hutt, Dr. G. Wetherley-Mein, Mr. W. A. Langmead, and **Dr. A. J. Grimes** (St. Thomas's Hospital):

Radioactive Iron Studies in Routine Hæmatological Practice

The value of iron tracer studies for research into normal and abnormal iron metabolism is well recognized. (Finch *et al.*, 1949; Huff *et al.*, 1950, 1951, 1953; Ledlie and Baxter, 1954; Badenoch and Callender, 1954). We have been principally concerned with the application of intravenous tracer techniques to routine hæmatological problems. Studies have been carried out in 80 patients with a variety of hæmatological disorders, and our object is to discuss briefly the interpretation and value of some of these results.

Following the intravenous injection of 10 μc of a tracer dose of iron we have used three techniques for following its metabolic pathways (Ledlie and Baxter, 1954).

(1) The plasma clearance. Iron is cleared exponentially from the plasma with a normal half clearance time of 70–120 minutes. Rapid half clearances are obtained as might be expected in hæmolytic anæmias, polycythæmia and in iron deficiency anæmia, and slow clearances when there is functional failure of erythropoiesis. However, these clearance times are partly dependent on the size of the labelled iron pool and also they are not simple functions and represent clearance to more than one organ. Their value as an assessment of erythropoietic function is, therefore, limited.

(2) Secondly, an estimate is made of the percentage of the total injected dose used for hæmoglobin synthesis. Utilization is maximal by the tenth day, and in the normal is between 70–80%. Utilization is lowered in functional erythropoietic failure, but this figure is again not an entirely reliable guide to red cell production as the results are modified by the size of the labelled plasma pool. This is shown by the apparently decreased utilization found in hæmochromatosis in spite of the normal marrow function. Furthermore, if there is hæmolysis with random red cell destruction the percentage utilization is low despite an increased red cell production. The reason for this is not entirely clear but is possibly due to iron entering a large, slowly turned-over pool in the reticulo-endothelial system.

(3) It is evident that both these techniques have some limitation as an assessment of erythropoietic function, and we have found that the addition of surface counting techniques adds considerably to the information.

Following the injection of iron, changes in activity are estimated over the sacrum, spleen, liver and heart using a directional scintillation counter without collimation. The activity is recorded directly on a ratemeter in counts per second.

In interpreting these results we are concerned principally with rate of change over each organ as there are considerable differences in counting conditions from organ to organ and from patient to patient.

Results

Normal.—The heart count falls as the plasma is cleared of iron, and at the same time the marrow count rises, reaching its peak at approximately thirty hours. There is then a gradual release of red cells containing Fe^{59} and the marrow count falls while the heart count rises. Red cell activity can be observed as early as five to ten hours and is maximal at seven to ten days. The spleen shows little significant change, and there is usually a small liver peak at about seven to ten hours, indicating a constantly turning over iron pool in this organ.

It is necessary to recognize that, like the plasma clearance and the iron utilization, these curves are liable to misinterpretation, for organ activity depends not only on iron in the specific organ iron pool but also on the activity of blood flowing through the organs.

Abnormal cases.—Certain well-defined patterns of abnormality are described to illustrate the value of these techniques.

(1) *Hypoplastic or aplastic type of anæmia.* These cases are characterized by a flat marrow curve together with a slowly ascending liver curve which reaches a peak between thirty-six and two hundred hours, indicating a slowly turned over, large iron pool in the liver. The plasma half-clearance is very slow and percentage utilization reduced.

(2) *Hæmolytic anæmia.* In these patients there is a rapid plasma clearance together with a rapid and high marrow uptake. The percentage utilization is low, and there is frequently a late splenic rise unaccounted for solely by blood activity and probably due to splenic destruction of red cells.

(3) *Extramedullary (splenic) erythropoiesis.* The striking feature of these cases is the rapid splenic rise reaching a peak at about thirty hours and then declining. The marrow curve is generally flat. The plasma clearance and percentage utilization depend on whether there is an accompanying hæmolysis.

Conclusions

These observations, which will be published in greater detail elsewhere, indicate that these techniques, particularly if combined with cell survival studies, enable one to obtain a dynamic picture of erythropoiesis which frequently allows a more rational approach to therapy.

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